

**Schlüsselfrage:**

**3.1 Patientenaufklärung**  
Fragestellung wurde 2016 durch IFOM aktualisiert, daher wurde in 2020 nur eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

**Inhalt: 2 Literaturstellen**

Literaturstelle	Evidenzlevel	Studientyp
Horn, A. 2020	2	SR
Powell, R. 2016	2	Systematic review and meta-analysis (105 studies)

**OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)**

Horn, A. et al. Preemptive and Preventive Pain Psychoeducation and Its Potential Application as a Multimodal Perioperative Pain Control Option: A Systematic Review. <i>Anesth Analg.</i> 130. 559-573. 2020			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level: 2</b></p> <p><b>Study type: SR</b></p> <p><b>Databases:</b> Medline, Google Scholar, and PubMed.</p> <p><b>Search period: 1955 to 2018</b></p> <p><b>Inclusion Criteria:</b> Individual case-controlled studies, original research studies, and systematic reviews; studies focussing on pain management education and postoperative recovery; studies involving cognitive-behavioral techniques; human studies, English language.</p> <p><b>Exclusion Criteria:</b> Expert opinion was excluded from the study.</p>	<p><b>Population:</b> Patients before treatment</p> <p><b>Intervention:</b> preoperative psychoeducational intervention</p> <p><b>Comparison:</b> -</p>	<p><b>Primary:</b> postoperative pain, outcomes to enhance recovery, prevent chronic postsurgical pain (CPSP), and minimize the opioid epidemic.</p> <p><b>Secondary:</b> -</p> <p><b>Results:</b> 43 studies included (24 trials from systematic search and 19 via handsearch).</p> <p><b>Preoperative Anticipated Pain Education (3 studies):</b> - strong evidence suggesting that pain expectation will have an impact on postoperative recovery.</p> <p><b>Procedural pain management (7 studies):</b> - procedural pain knowledge has a significant impact on pain control and recovery time, and patients who opted out of procedural pain education had longer hospitalization and poor pain management.</p> <p><b>Anxiety and Pain Catastrophizing Effect (9 studies):</b> - strong negative relationship between preoperative anxiety/pain catastrophizing and postoperative recovery.</p> <p><b>Information delivery strategy (3 studies):</b> - The way health care providers address patients and present psychoeducational pain information should be considered. An open and sympathetic discussion between providers and patients is crucial for optimal satisfaction and maximum recovery.</p> <p><b>Psychoeducational cost (3 studies):</b></p>	<p>see publication.</p>

- implementing psychoeducation could decrease health care costs.

Author's Conclusion:

**Methodical Notes**

Funding Sources: Departmental/institutional.

COI: Nothing to declare.

Study Quality: The quality of evidence obtained from the literature searches was then assessed and graded using the Oxford levels of evidence.

Heterogeneity: n.a.

Publication Bias: not assessed.

**Notes:**

Oxford CEBM Level of Evidence: EL 2 (systematic review) Downgraded one level, due to methodological weaknesses.

**Limits:**

- population unclear (patients before and after surgery?)
- comparison unclear
- study design and compared procedures are diverse,

Powell, R. et al. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Database of Systematic Reviews. . . 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review and meta-analysis (105 studies) Databases: Cochrane Central; MEDLINE; EMBASE; PsycINFO; CINAHL (EBSCOhost) ; Dissertation Abstracts and ISI Web of Science.</p> <p>Search period: 2014</p> <p>Inclusion Criteria: We included randomized controlled trials of adult participants (aged 16 or older) undergoing elective surgery under general anaesthesia. We did not limit the search by language or publication status. We included studies testing a preoperative psychological intervention that included at least one of these seven techniques: procedural information; sensory information; behavioural instruction; cognitive intervention; relaxation techniques; hypnosis; emotion-focused intervention. We included studies that examined any one of our postoperative outcome measures (pain, behavioural recovery, length of stay, negative aBect) within one month post-surgery.</p> <p>Exclusion Criteria: Studies focusing on patient groups with clinically diagnosed psychological morbidity.</p>	<p>Population: adult participants (aged 16 or older) undergoing elective surgery under general anaesthesia.</p> <p>Intervention: 1. procedural information; 2. sensory information; 3. behavioural instruction; 4. cognitive interventions; 5. relaxation techniques; 6. hypnosis; 7. emotion-focused interventions.</p> <p>Comparison: any</p>	<p>Primary: 1. Postoperative pain 2. Behavioural recovery*</p> <p>Secondary: 1 Negative affect* 2. Length of stay in hospital (days)</p> <p>Results: Only postoperative pain outcome summary available in this section due to length. Other outcomes see article. <u>Summary: postoperative pain</u> Sixty-one studies assessed the outcome postoperative pain. It was possible to include data for 38 studies (36% of 105 studies) with analysis of 2713 participants' data (26% of 10.302 participants randomized across all studies). In summary, the pattern of evidence from the meta-analyses suggests that psychological preparation may reduce postoperative pain in the first month aPer surgery, although this finding should be treated with caution since it is based on pooling studies with diverse types of psychological interventions and because the size of the pooled effect (-0.20) would generally be considered of low magnitude (Cohen 1988). Of the narratively synthesized studies, most found no significant difference between intervention and control groups. It is of interest that, while none of these studies contained 'pure' behavioural instruction, 12 of the 16 studies reporting non-significant differences contained behavioural instruction as a component. This would be consistent with the meta-analysis findings suggesting that behavioural instruction does not impact postoperative pain. However, similarly to the studies in the meta-analyses, there is a high degree of heterogeneity in these studies in terms of the types of surgery and intervention content. Due to the high heterogeneity, and the high</p>	<p>105 articles included, see article for details.</p>

number of studies reporting sufficient methodological details to ascertain risk of bias, we downgraded the overall quality of evidence for the outcome postoperative pain by two points to 'low'.

**Author's Conclusion:** The evidence suggested that psychological preparation may be beneficial for the outcomes postoperative pain, behavioural recovery, negative affect and length of stay, and is unlikely to be harmful. However, at present, the strength of evidence is insufficient to reach firm conclusions on the role of psychological preparation for surgery. Further analyses are needed to explore the heterogeneity in the data, to identify more specifically when intervention techniques are of benefit. As the current evidence quality is low or very low, there is a need for well-conducted and clearly reported research.

#### Methodical Notes

##### Funding Sources: Internal sources

- Manchester Centre for Health Psychology, University of Manchester, UK.

An award of £2000 was received to support research assistant costs.

##### External sources

- British Academy, UK.

We received a small research grant of £7480 to support research assistant costs.

COI: declared, see article for details.

##### Study Quality: Risk of bias assesment for each study and GRADE Sof for each outcome.

Generally, the evidence suffered from poor reporting, meaning that few studies could be classified as having low risk of bias.

Overall, we rated the quality of evidence for each outcome as 'low' because of the high level of heterogeneity in meta-analysed studies and the unclear risk of bias. In addition, for the outcome behavioural recovery, too few studies used robust measures and reported suitable data for metaanalysis, so we rated the quality of evidence as 'very low'.

**Heterogeneity:** "High heterogeneity was also a problem, particularly in the varying content of interventions. Rather than simply label all interventions as being 'psychological' we classified them into seven groups, which has enabled us to demonstrate the high level of variation across interventions. There was also heterogeneity in the wide range of surgery types participants underwent."

We have reported meta-analysis findings despite high levels of heterogeneity, which limits the confidence that can be placed in the findings. We believe that this is, however, helpful, as this is a large review and summarizing data in this way allows the findings to be more easily interpreted than placing so many studies in a table. In addition, as many studies contained small samples and

individual results were often not statistically significant, combining studies allows a helpful picture of the potential of interventions."

**Publication Bias:** Publication bias was investigated using funnel plots. "The funnel plots for the individual outcomes showed no clear evidence of publication bias."

##### Notes:

Oxford level of evidence: 2 systematic review and meta-analysis (downgraded one level).

High level of heterogeneity is reported, but discussed and investigated.

Schlüsselfrage:

3.3.1.1 Psychologische Verfahren

Fragestellung wird durch LL-Adaptation aktualisiert. Zusätzlich wurde in 2020 eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

Inhalt: 6 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Laopaiboon, M. 2009	1	Systematic review and meta-analysis (1 study included).
Powell, R. 2016	2	Systematic review and meta-analysis (105 studies)
Renner, R. M. 2009	1	Systematic review and meta-analysis (40 studies included).
Sado, M. 2012	1	Systematic review (1 study included).
Smith, C. A. 2018	1	Systematic review and meta-analysis.
Ziehlm, S. 2017	1	Systematic review and meta-analysis (23 studies)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 6 Bewertung(en)

Laopaiboon, M. et al. Music during caesarean section under regional anaesthesia for improving maternal and infant outcomes. Cochrane Database of Systematic Reviews. . . 2009			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (1 study included).</p> <p>Databases: The Cochrane Pregnancy and Childbirth Group's Trials Register consisting of</p> <ol style="list-style-type: none"> <li>quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);</li> <li>weekly searches of MEDLINE;</li> <li>handsearches of 30 journals and the proceedings of major conferences;</li> <li>weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.</li> </ol> <p>Search period: 09.2008</p> <p>Inclusion Criteria: We included randomised controlled trials comparing music added to standard</p>	<p>Population: Pregnant women scheduled to receive caesarean sections under regional anaesthesia.</p> <p>Intervention: Addition of any type of music to routine care during caesarean section.</p> <p>Comparison: Routine care alone during caesarean section.</p>	<p>Primary: For mothers</p> <ol style="list-style-type: none"> <li>Pain intensity (self-report measured with the visual analogue scale during and after caesarean section)</li> <li>Analgesic requirement during and after caesarean section</li> <li>Anxiety during and after caesarean section as defined by investigators</li> <li>Maternal death</li> <li>Clinical outcomes <ul style="list-style-type: none"> <li>5.1 Blood pressure</li> <li>5.2 Pulse haemoglobin oxygen saturation (SpO2)</li> <li>5.3 Respiratory rates</li> <li>5.4 Heart rate and its variability</li> <li>5.5 Blood loss</li> <li>5.6 Immediate postoperative complications</li> </ul> </li> </ol> <p>For infants</p> <ol style="list-style-type: none"> <li>Apgar scores at one and five minutes</li> <li>Birth asphyxia</li> <li>Infant death</li> </ol> <p>Secondary: For mothers</p> <ol style="list-style-type: none"> <li>Maternal satisfaction</li> <li>Injury from surgical procedures such as urinary bladder injury, vessel injury, etc</li> <li>Skin to skin contact between mother and infant during or after caesarean section</li> <li>Breastfeeding initiation and duration</li> </ol> <p>For infants</p> <ol style="list-style-type: none"> <li>Injury from surgical procedures such as cut wound, etc</li> <li>Physical and psychological development of infants as defined by investigators</li> </ol> <p>Results: "It appears that music added to standard care during caesarean section under regional anaesthesia had some impact on pulse rate at the end of maternal contact with the neonate in the intra-operative period (MD -7.50 fewer beats per minute, 95% CI -14.08 to -0.92) and after completion of skin suture for the caesarean section (MD -7.37 fewer beats per minute, 95% CI -13.37 to -1.37). There was also an</p>	<p>Chang 2005,</p>

care during caesarean section under regional anaesthesia to standard care alone.

**Exclusion Criteria:**  
One study was excluded because caesarean section was performed under general anaesthesia.

improvement in the birth satisfaction score (maximum possible score of 35) (MD of 3.38, 95%CI 1.59 to 5.17). Elects on other outcomes were either not significant or not reported in the one included trial."

**Author's Conclusion:** The findings of this review indicate that music during caesarean section under regional anaesthesia may have positive effects on pulse rates and birth satisfaction of mothers. However, the poor methodological quality of the one included study makes it impossible to draw any firm conclusions about the electiveness of music during caesarean section under regional anaesthesia for improving maternal and infant outcomes.

**Methodical Notes**

**Funding Sources:** Internal sources

- Faculty of Public Health, Khon Kaen University, Thailand.
- Faculty of Medicine, Khon Kaen University, Thailand.
- Faculty of Nursing, Khon Kaen University, Thailand.
- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

**External sources**

- Thailand Research Fund (Senior Research Scholar), Thailand.
- SEA-ORCHID project, Not specified.

**COI:** None known.

**Study Quality:** Malinee Laopaiboon (ML) and Ruth Martis (RM) independently assessed risk of bias for the included study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

The one included trial was assessed as having 'unclear' information in five domains of risk of bias: sequence generation; allocation concealment; blinding; free selective reporting; and free other risk of bias and was considered was of low quality.

**Heterogeneity:** We will assess heterogeneity using the I2 statistic. If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis.

We will conduct subgroup analyses classifying for potential sources of heterogeneity including ethnic groups, types of music (i.e. mother's or investigator's preference and genre), methods of music delivery (via loudspeakers or headphone), elective versus emergency caesarean section, and primary versus multiple caesarean section, where sulicient data are available.

**Publication Bias:** "We will consider publication bias using funnel plots of between-treatment effect and its precision on individual trials, and Egger's test. If we find asymmetrical funnel plots with statistical publication bias, we will further examine the effect of the bias on the meta-analysis conclusion using sensitivity analyses."

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Notes: Article is of limited evidence, as it includes only one study which was considered to be of low evidence.

**Powell, R. et al. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Database of Systematic Reviews. . . 2016**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level:</b> 2</p> <p><b>Study type:</b> Systematic review and meta-analysis (105 studies)</p> <p><b>Databases:</b> Cochrane Central; MEDLINE; EMBASE; PsycINFO; CINAHL (EBSCOhost) ; Dissertation Abstracts and ISI Web of Science.</p> <p><b>Search period:</b> 2014</p> <p><b>Inclusion Criteria:</b> We included randomized controlled trials of adult participants (aged 16 or older) undergoing elective surgery under general anaesthesia. We did not limit the search by language or publication status. We included studies testing a preoperative psychological intervention that included at least one of these seven techniques: procedural information; sensory information; behavioural instruction; cognitive intervention; relaxation techniques; hypnosis; emotion-focused intervention. We included studies that examined any one of our postoperative outcome measures (pain, behavioural recovery, length of stay, negative</p>	<p><b>Population:</b> adult participants (aged 16 or older) undergoing elective surgery under general anaesthesia.</p> <p><b>Intervention:</b> 1. procedural information; 2. sensory information; 3. behavioural instruction; 4. cognitive interventions; 5. relaxation techniques; 6. hypnosis; 7. emotion-</p>	<p><b>Primary:</b> 1. Postoperative pain 2. Behavioural recovery*</p> <p><b>Secondary:</b> 1 Negative affect* 2. Length of stay in hospital (days)</p> <p><b>Results:</b> Only postoperative pain outcome summary available in this section due to length. Other outcomes see article. <u>Summary: postoperative pain</u> Sixty-one studies assessed the outcome postoperative pain. It was possible to include data for 38 studies (36% of 105 studies) with analysis of 2713 participants' data (26% of 10.302 participants randomized across all studies). In summary, the pattern of evidence from the meta-analyses suggests that psychological preparation may reduce postoperative pain in the first month aPer surgery, although this finding should be treated with caution since it is based on pooling studies with diverse types of psychological interventions and because the size of the pooled effect (-0.20) would generally be considered of low</p>	<p>105 articles included, see article for details.</p>

<p>aBect) within one month post-surgery.</p> <p><b>Exclusion Criteria:</b> Studies focusing on patient groups with clinically diagnosed psychological morbidity.</p>	<p>focused interventions.</p> <p>Comparison: any</p>	<p>magnitude (Cohen 1988). Of the narratively synthesized studies, most found no significant difference between intervention and control groups. It is of interest that, while none of these studies contained 'pure' behavioural instruction, 12 of the 16 studies reporting non-significant differences contained behavioural instruction as a component.</p> <p>This would be consistent with the meta-analysis findings suggesting that behavioural instruction does not impact postoperative pain. However, similarly to the studies in the meta-analyses, there is a high degree of heterogeneity in these studies in terms of the types of surgery and intervention content. Due to the high heterogeneity, and the high number of studies reporting sufficient methodological details to ascertain risk of bias, we downgraded the overall quality of evidence for the outcome postoperative pain by two points to 'low'.</p> <p><b>Author's Conclusion:</b> The evidence suggested that psychological preparation may be beneficial for the outcomes postoperative pain, behavioural recovery, negative affect and length of stay, and is unlikely to be harmful. However, at present, the strength of evidence is insufficient to reach firm conclusions on the role of psychological preparation for surgery. Further analyses are needed to explore the heterogeneity in the data, to identify more specifically when intervention techniques are of benefit. As the current evidence quality is low or very low, there is a need for well-conducted and clearly reported research.</p>
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**Methodical Notes**

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**COI:** declared, see article for details.

**Study Quality:** Risk of bias assesment for each study and GRADE Sof for each outcome. Generally, the evidence suffered from poor reporting, meaning that few studies could be classified as having low risk of bias. Overall,we rated the quality of evidence for each outcome as 'low' because of the high level of heterogeneity in meta-analysed studies and the unclear risk of bias. In addition, for the outcome behavioural recovery, too few studies used robust measures and reported suitable data for metaanalysis, so we rated the quality of evidence as 'very low'.

**Heterogeneity:** "Hig heterogeneity was also a problem, particularly in the varying content of interventions. Rather than simply label all interventions as being 'psychological' we classified them into seven groups, which has enabled us to demonstrate the high level of variation across interventions. There was also heterogeneity in the wide range of surgery types participants underwent."

We have reported meta-analysis findings despite high levels of heterogeneity, which limits the confidence that can be placed in the findings. We believe that this is, however, helpful, as this is a large review and summarizing data in this way allows the findings to be more easily interpreted than placing so many studies in a table. In addition, as many studies contained small samples and individual results were often not statistically significant, combining studies allows a helpful picture of the potential of interventions."

**Publication Bias:** Publication bias was investigated using funnel plots. "The funnel plots for the individual outcomes showed no clear evidence of publication bias."

**Notes:**  
Oxford level of evidence: 2 systematic review and meta-analysis (downgraded one level).  
High level of heterogeneity is reported, but discussed and investigated.

level/Study Types			
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (40 studies included).</p> <p>Databases: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, POPLINE.</p> <p>Search period: Inception - 2008</p> <p>Inclusion Criteria: Randomized controlled trials comparing methods of pain control in first trimester surgical abortion at less than 14 weeks gestational age using electric or manual suction aspiration. Outcomes included intra- and postoperative pain, side effects, recovery measures and satisfaction.</p> <p>Exclusion Criteria: -</p>	<p>Population: Pregnant women undergoing first trimester surgical abortion at less than 14 weeks gestational age using electric or manual suction aspiration.</p> <p>Intervention: Any type of pharmacological pain control administered via mucosal (oral, vaginal, intrauterine, buccal/sublingual), intramuscular, or intravenous routes or non-pharmacological pain control prior to or during a first trimester surgical abortion at less than 14 weeks gestational age using electric or manual suction aspiration.</p> <p>Comparison: each other intervention.</p>	<p>Primary: The main outcome is patient reported effectiveness of pain control on perceived pain during and immediately post abortion using validated scales, e.g. visual analogue, CAT, and Likert scales, categorical or dichotomous assessment (yes versus no). Additional outcomes are adverse effects, and side effects (including if the method of pain control causes pain), as well as patient satisfaction.</p> <p>Secondary: no distinction between primary and secondary outcomes.</p> <p>Results: 40 studies met inclusion criteria with a total of 5131 participants. <a href="#">Only summary results are available here due to length.</a></p> <p>Due to heterogeneity we divided studies into 7 groups:</p> <p>Local anesthesia: Data was insufficient to show a clear benefit of a paracervical block (PCB) compared to no PCB or a PCB with bacteriostatic saline. Pain scores during dilation and aspiration were improved with deep injection (WMD -1.64 95% CI -3.21 to -0.08; WMD 1.00 95% CI 1.09 to 0.91), and with adding a 4% intrauterine lidocaine infusion (WMD -2.0 95% CI -3.29 to -0.71, WMD -2.8 95% CI -3.95 to -1.65 with dilation and aspiration respectively).</p> <p>PCB with premedication: Ibuprofen and naproxen resulted in small reduction of intra- and post-operative pain.</p> <p>Analgesia: Diclofenac-sodium did not reduce pain.</p> <p>Conscious sedation: The addition of conscious intravenous sedation using diazepam and fentanyl to PCB decreased procedural pain.</p> <p>General anesthesia (GA): Conscious sedation increased intraoperative but decreased postoperative pain compared to GA (Peto OR 14.77 95% CI 4.91 to 44.38, and Peto OR 7.47 95% CI 2.2 to 25.36 for dilation and aspiration respectively, and WMD 1.00 95% CI 1.77 to 0.23 postoperatively). Inhalation anesthetics are associated with increased blood loss (p&lt;0.001).</p> <p>GA with premedication: The COX 2 inhibitor etoricoxib, the non-selective COX inhibitors lornoxicam, diclofenac and ketorolac IM, and the opioid nalbuphine were improved postoperative pain.</p> <p>Non-pharmacological intervention: Listening to music decreased procedural pain.</p> <p>No major complication was observed.</p> <p>Author's Conclusion: Implications for practice</p> <p>Methods of pain control including local anesthesia, IV sedation, general anesthesia and non-pharmacological methods for first trimester surgical abortion have been studied. Many have been found to effectively decrease pain during and after the procedure while being safe and satisfactory to patients. No major complications were observed in any study. Many patients still find the procedure extremely uncomfortable due to pain with</p>	<p>40 studies, Barneschi 1985, Bone 1988, Bonnardot 1987, Boysen 1989, Boysen 1990, Cetin 1997, Collins 1985, Dahl 2000, Edelman 2004, Edelman 2006, Glantz 2001, Hackett 1982, Hall 1997, Heath 1989, Hein 1999, Hein 2001, Jakobsson 1991, Jakobsson 1993, Jakobsson 1995, Jakobsson 1996, Kan 2004, Kan 2006, Li 2003, Li 2006, Lindholm 1994, Marc 2007, Ogg 1983, Phair 2002, Raeder 1992, Rossi 1995, Shapiro 1975, Suprpto 1984, Wells 1989, Wells 1992, Wiebe 1992, Wiebe 1995, Wiebe 1996, Wiebe 2003, Wong 2002</p>

cervical dilation and aspiration, unless given general anesthesia. Given how widely used the PCB is, the paucity of data supporting the benefit of a PCB as shown in this review is surprising and concerning.

Given these findings, factors such as women's preference, medical risk factors for anesthesia complications, setting and resources availability should be considered when choosing a method of pain control. Trials were too heterogeneous to be combined in a large meta-analysis.

Considering the small WMD of some significant results, as well as the quality of evidence the strongest evidence supports:

- 1) Data on the effect of a PCB and buffered lidocaine are conflicting. PCB with local anesthetic such chlorprocaine reduced pain with PCB injection, cervical dilation and aspiration in only one small study, and only when injected at 4 sites, but not when injected at only 2 sites. Another study did not show any benefit of a PCB over no PCB. A deep injection technique seems to reduce pain with cervical dilation and aspiration. Strong evidence supports adding intrauterine 4% lidocaine, but one must be prepared for patients reporting lidocaine exposure symptoms (i.e. ear ringing).
- 2) Conscious sedation combined with PCB do not achieve the same pain control as general anesthesia during the procedure, but improved postoperative pain control.
- 3) General anesthesia ideally consists of a combination of propofol (methohexital, etomidate and thiopentane had very similar results, but have fallen out of favour in many places by now for procedural pain control) with an opioid for postoperative pain control.
- 4) Premedication for general anesthesia: lornoxicam, IM ketorolac or diclofenac.

#### Methodical Notes

##### Funding Sources: Internal sources

- Dept. of Obstetrics and Gynaecology, Oregon Health and Science University, Portland, USA, Not specified. Library services.

##### External sources

- No sources of support supplied

COI: Several declared, see article.

Study Quality: Study quality was investigated and reported according to the Cochrane handbook.

Heterogeneity: "Trials were too heterogeneous to be combined in a large meta-analysis." Due to heterogeneity we divided studies into 7 groups for comparisons.

Publication Bias: publication bias not investigated.

##### Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.

Publication bias not investigated.

Sado, M. et al. Hypnosis during pregnancy, childbirth, and the postnatal period for preventing postnatal depression. Cochrane Database of Systematic Reviews. . . 2012

Evidence Types	level/Study	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review (1 study included). Databases: Cochrane		Population: All pregnant women, women in labour, or new mothers to whom hypnosis	Primary: 1. The development of PND (defined as a score of more than 12 on the Edinburgh Postnatal Depression Scale or as a diagnosis by way of a structured diagnostic interview).	Harmon, 1990, Improved obstetric outcomes using hypnotic analgesia and skill mastery



<p>Pregnancy and Childbirth Group's Trials Register which contains trials from 1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); 2. weekly searches of MEDLINE; 3. weekly searches of EMBASE; 4. handsearches of 30 journals and the proceedings of major conferences; 5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.</p> <p>Search period: Inception - 2011</p> <p>Inclusion Criteria: Randomised controlled trials comparing hypnosis with usual antenatal, intranatal, or postnatal care, where the primary or secondary objective is to assess whether there is a reduced risk of developing postnatal depression.</p> <p>Exclusion Criteria: Studies were excluded if they had used a quasirandomised design.</p>	<p>was delivered antenatally, intranatally, or within the first postnatal month.</p> <p>Intervention: Hypnosis provided to pregnant women, women in labour, or new mothers within the first postnatal month</p> <p>Comparison: Usual antenatal, intranatal, or postnatal care.</p>	<p>Secondary: 1. Development of postnatal psychosis. 2. Postnatal anxiety disorder. 3. Maternal mortality and serious morbidity including outpatient and inpatient use of psychiatric units, or other health services. 4. Maternal-infant attachment. 5. Suicidal ideation. 6. Death by suicide within one year of the birth.</p> <p>Results: One study included in the analysis, Only the MMPI Depression scale mean scores were reported, and no data were provided regarding whether or not hypnosis reduced the risk of developing PND; therefore, this study was assessed as being unable to contribute to this review and no further analyses were performed.</p> <p>For reference, in the trial, first, the participants were divided into two groups according to their hypnotic susceptibility (high and low). Then, the participants in each group were randomly allocated to the hypnosis or control group respectively (two treatment conditions x two susceptibility separations). The mean score on the MMPI Depression scale in the highly susceptible hypnosis group was lower than that for the other three groups combined.</p> <p>Author's Conclusion: Implications for practice Although some trials have been undertaken which indicate the possibility that hypnosis may be effective when it comes to reducing depressive symptoms, as yet, there is no evidence available from randomised controlled trials which shows the effectiveness of hypnosis for preventing the development of PND.</p>	<p>combined with childbirth education. Journal of Consulting and Clinical Psychology 1990;58:525-30.</p>
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<p><b>Methodical Notes</b></p>
<p><b>Funding Sources:</b> Internal sources • Keio University School of Medicine, Tokyo, Japan. External sources • No sources of support supplied</p> <p><b>COI:</b> None known.</p> <p><b>Study Quality:</b> For the one included study the risk of bias was assessed separately by two review authors using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. One RCT was included in this review. The risk of bias in the study was unclear because all factors other than blinding (allocation sequence, allocation concealment, incomplete outcomes and being free of suggestion of selective outcome reporting) were unclear.</p> <p><b>Heterogeneity:</b> In each meta-analysis we will assess statistical heterogeneity by using the TZ, IZ and Chi2 test statistics. If the IZ statistic is greater than 30% and either TZ is greater than zero, or there is a low P value (less than 0.10) on the Chi2 test for heterogeneity, then heterogeneity will be regarded as being substantial.</p> <p><b>Publication Bias:</b> Funnel plots will be used to provide information on reporting biases (such as publication bias) if the meta-analysis consists of 10 or more studies. A visual assessment will be made of funnel plot asymmetry in conjunction with more formal tests for funnel plot asymmetry.</p> <p><b>Notes:</b> Oxford level of evidence: 1 Systematic review. Article might be of limited value, due to the fact that only a single study is included. The use of a trials register which includes data from other databases in this case is easier to conduct but likely excludes some articles.</p>

<p>Smith, C. A. et al. Relaxation techniques for pain management in labour. Cochrane Database of Systematic Reviews. . . 2018</p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1 Study type: Systematic review and meta-analysis. Databases: Cochrane Pregnancy</p>	<p>Population: Women in labour. (This will include women in high-risk groups, e.g.</p>	<p>Primary: <u>Effects of interventions</u> 1. Pain intensity (as defined by trialists). We will analyse pain by the phase of labour if reported. 2. Satisfaction with pain relief (as</p>	<p>15 articles in total included. Alemeida 2005, Bagharpoosh 2006, Bahadoran 2010,</p>

and Childbirth's Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL, the Australian New Zealand Clinical Trials Registry (18 May 2017), ClinicalTrials.gov, the ISRCTN Register, the WHO International Clinical Trials Registry Platform (ICTRP), and reference lists of retrieved studies.

Search period: Inception to 05/2017

**Inclusion Criteria:** Randomised controlled trials (including quasi randomised and cluster trials) comparing relaxation methods with standard care, no treatment, other non-pharmacological forms of pain management in labour or placebo.

**Exclusion Criteria:** Cross-over trials were excluded.

preterm labour or following induction of labour.

**Intervention:** 1. Placebo/no treatment

2. Hypnosis (Madden 2016)
3. Biofeedback (Barragán 2011)
4. Intracutaneous or subcutaneous sterile water injection (Derry 2011)
5. Immersion in water (Cluett 2009)
6. Aromatherapy (Smith 2011b)
7. Relaxation techniques (yoga, music, audio) (this review)
8. Acupuncture or acupressure (Smith 2011a)
9. Manual methods (massage, reflexology) (Smith 2011c)
10. Transcutaneous electrical nerve stimulation (TENS) (Dowswell 2009)
11. Inhaled analgesia (Klomp 2011)
12. Opioid drugs (Ullman 2010)
13. Non-opioid drugs (Othman 2011)
14. Local anaesthetic nerve blocks (Novikova 2011)
15. Epidural (including combined spinal-epidural) (Anim-Somuah 2005; Simmons 2007)

**Comparison:** placebo, standard care, no treatment, other non-pharmacological forms of pain management

defined by trialists)

3. Sense of control in labour (as defined by trialists)

4. Satisfaction with childbirth experience (as defined by trialists)

Safety of interventions

1. Elect (negative) on mother/baby interaction
2. Breastfeeding (at specified time points)
3. Assisted vaginal birth
4. Caesarean section
5. Side effects (for mother and baby; review specific)
6. Admission to special care nursery or neonatal intensive care (as defined by trialists)
7. Low Apgar score (less than 7 at five minutes)
8. Poor infant outcomes at long-term follow-up (as defined by trialists)

Other outcomes

1. Cost (as defined by trialists)

**Secondary:** Use of pharmacological pain relief; length of labour; spontaneous vaginal birth; need for augmentation with oxytocin; perineal trauma (defined as episiotomy and incidence of second- or third-degree tear); maternal blood loss (postpartum haemorrhage defined as greater than 500 mL); anxiety.

**Results:** Only pain outcomes described here, due to length, other outcomes see article.

**Study Population:** 19 studies involving 2519 women

**Results:**

1) Relaxation 10 trials, 7 of which in MA

1.1.1 Latent phase

Yildirim 2004 found a reduction in pain intensity (using a 10-point visual analogue scale (VAS)) for women receiving instruction on relaxation during the latent phase (mean difference (MD) -1.25, 95% confidence interval (CI) -1.97 to -0.53, 40 women).

1.1.2 Active phase

The effect of relaxation on pain intensity during the active phase of labour (using a 10-point VAS) was not clear; due to high heterogeneity between trials we used a random-effects model (MD -1.08, 95% CI -2.57 to 0.41, four trials, 271 women, IU = 90%, TauU = 1.99, very low-quality evidence) (Analysis 1.1). The heterogeneity was explained primarily by Yildirim 2004, and potentially by the bias introduced from unclear randomisation and high risk of bias in relation to blinding.

1.2) Pain intensity (at follow-up)

This assessment of pain intensity was assessed at follow-up. There was no clear evidence of a difference between groups in maternal perception of pain (assessed along a Likert scale, where 0 indicated 'no pain at all' and 7 was 'worst imaginable pain'). (MD -0.00, 95% CI -0.23 to 0.23, one trial, 977 women)

Bergstrom 2009,  
Boaviagem 2017,  
Chuntharapat 2008,  
Dizavandi 2012, Dolectta 1979,  
Duncan 2017,  
Durham 1986, Gatelli 2000,  
Gedde-Dahi 2012,  
Hosseinei 2013, Kimber 2008,  
Liu 2010, Moore 1965,  
Phumdoung 2007,  
Simavli 2014, Yildirim 2004.

1.3) Satisfaction with pain relief in labour There was increased satisfaction with pain relief for women receiving relaxation compared with the control (risk ratio (RR) 8.00, 95% CI 1.10 to 58.19, one trial, 40 women, very low-quality evidence).

2) Yoga 2 trials and 149 women in the meta-analysis.

#### 2.1) Pain intensity

There was lower pain intensity reported by women (VAS 0 to 100) in the latent phase for women receiving yoga compared with the control group (MD -6.12, 95% CI -11.77 to -0.47, one trial, 66 women, low-quality evidence).

#### 2.2) Satisfaction with pain relief

There was greater satisfaction (assessed with a visual analogue sensation of pain scale ) with pain relief for women receiving yoga compared with the control (MD 7.88, 95% CI 1.51 to 14.25, one trial, 66 women, low-quality evidence).

3) Music We included 5 trials for this intervention, n=2177

#### 3.1) Pain intensity

##### 3.1.1 Latent phase

There was evidence of lower pain scores (VAS 0 to 10) in the music group in the latent phase (MD -0.73, 95% CI -1.01 to -0.45, random effects, two trials, 192 women) (Analysis 3.1).

##### 3.1.2 Active phase

There was no strong evidence that pain scores differed between groups (VAS 0 to 10) in the music group in the active phase (MD -0.51, 95% CI -1.10 to 0.07, random-effects, 217 women, three studies, substantial heterogeneity  $I^2 = 67\%$ ,  $Tau^2 = 0.15$ , very low quality evidence). The heterogeneity was explained by Simavli 2014 and the influence of high risk of bias on several domains.

##### 3.1.3 Transition phase

During transition there were lower pain scores (0 to 10 VAS) in the relaxation group (MD -0.70, 95% CI -0.86 to -0.54, one trial, 132 women) (Analysis 3.1).

4) Audio-analgesia 1 trial of 24 women was included in the meta-analysis in a comparison with white noise.

#### Satisfaction with pain relief

There was no clear evidence of a difference between groups (RR 2.00, 95% CI 0.82 to 4.89, one trial, 24 women).

**Author's Conclusion:** The limited data available suggested that relaxation modalities may be a helpful modality for pain management in labour and there is no evidence of harm; however, there is insufficient evidence to inform clinical practice. Overall there are insufficient data to demonstrate whether relaxation modalities prove an additive

benefit when used in combination with usual care, or whether they are more elective than usual care. Due to the unknown risk of bias of in the majority of trials and limited number of trials, further high quality research is needed.

### Methodical Notes

#### Funding Sources: Internal sources

- NICM, Western Sydney University, Australia.
- Women's and Children's Health Research Institute, Flinders Medical Centre South Australia, Australia.
- Children, Youth and Women's Health Services, Adelaide, Australia.
- The University of Adelaide, Adelaide, Australia.

#### External sources

- WHO UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

COI: numerous, see article.

**Study Quality:** For this update we assessed the quality of the evidence using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence for the following outcomes.

**Heterogeneity:** We assessed statistical heterogeneity in each meta-analysis using the TauU, IU (Higgins 2003) and ChiU statistics (Deeks 2011). We regarded heterogeneity as substantial if IU was greater than 30% and either TauU was greater than zero, or there was a low P value (less than 0.10) in the ChiU test for heterogeneity. If we identified substantial heterogeneity (above 30%), provided sufficient data were available, we planned to explore it by pre-specified subgroup analysis.

**Publication Bias:** Not investigated. "In future updates, if there are 10 or more studies in the metaanalysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it (Sterne 2011)."

#### Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.

Ziehm, S. et al. Psychological interventions for acute pain after open heart surgery. Cochrane Database of Systematic Reviews. . . 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (23 studies)</p> <p>Databases: • CENTRAL (the Cochrane Library) February 2017; • MEDLINE (OVID), Sept 2013 to February week 1, 2017; • Embase (OVID), Sept 2013 to week 5, 2017; • Web of Science (ISI), 2013 to 31 January 2017; • PsycINFO (OVID), 2013 to January week 4, 2017; • ProQuest Dissertations and Theses Full Text Database,</p>	<p>Population: Adult participants (men and women aged 18 and over) undergoing open heart surgery (valve procedures with or without cardiopulmonary bypass (CPB), coronary surgery with or without CPB, congenital lesion, surgery of thoracic aorta, other cardiac surgery, e.g. resection of heart neoplasm and assist devices). We included participants independent of their pre- and postoperative mental health status.</p> <p>Intervention: psychological interventions provided within the time of hospitalisation:</p> <ul style="list-style-type: none"> <li>• psychoeducational interventions;</li> <li>• cognitive-behavioural methods;</li> <li>• relaxation techniques</li> </ul> <p>Comparison: • 'treatment as usual' (TAU), defined as the standard care of the hospital with no psychological intervention provided to the control group. • 'attention control', defined as providing the same amount of time and attention, but with no specific psychological</p>	<p>Primary: 1. Number of participants with self-reported pain intensity reduction of at least 50% from baseline. 2. Number of participants below 30/100 mm on the visual analogue scale (VAS) in self-reported postoperative pain intensity. 3. Participant-reported postoperative pain intensity measured on continuous or categorical scales, or other participant-reported. 4. pain intensity scales or questionnaires with satisfactory reliability and validity.</p> <p>Secondary: 1. Observer-reported postoperative median time to remedication. 2. Observer-reported postoperative number of participants re-medicated. 3. Observer-reported postoperative analgesic use measured via participant-controlled analgesia (PCA), with conversion into morphine equivalents. 4. Participant-reported postoperative mental distress (defined as negative affect, anxiety, depression, mood, well-being, relaxation) rating scales with satisfactory reliability and validity. 5. Participant- and observer-reported postoperative levels of mobility measured via, for example, the six-minute walk test. 6. Observer-reported time to extubation.</p> <p>Results: Only main comparison outcomes reported here due to length. Other outcomes see article.</p>	<p>23 studies: Akgul 2016; Bergmann 2001, Dao 2011, De Klerk 2004, Deyirmnjan 2006, Gillies 1993, Guo 2012, Heilmann 2016, Hoseine 2013, Ku 2002, Mahler 1998, Mahler 1999, Martorella 2012, Moore 2001, Parent 2000, Parthum 2006, Pick 1994, Rief 2017, Shelley 2007, Sorlie 2007, Utriyaaprasit 2010, Zarani 2010, Zarea 2014.</p>

<p>Search period: 2013 (previous version) - 02/2017</p> <p>Inclusion Criteria: Randomised controlled trials comparing psychological interventions as an adjunct to standard care versus standard care alone or standard care plus attention in adults undergoing open heart surgery.</p> <p>Exclusion Criteria: We excluded studies on emergency procedures and heart transplantation because participants differ in disease severity and time to be psychologically prepared for surgery, among other factors.</p>	<p>intervention offered to the control group</p>	<p>Main comparison: <u>Psychological interventions versus control condition</u> We included 23 trials (2669 participants) comparing psychological interventions against a control condition. <u>Number of participants with self-reported pain intensity reduction of at least 50% from baseline.</u> Number of participants below 30/100 mm on visual analogue scale (VAS) in self-reported postoperative pain intensity Data on the number of participants below 30/100 mm on VAS pain intensity in the short term were only provided by one study (73 participants; Parthum 2006). Psychological interventions did not reduce pain intensity below 30/100 mm on the Visual Analogue Scale: risk ratio (RR) 1.20 (95% confidence interval (CI) 0.68 to 2.12). The number needed to treat for one additional beneficial outcome (NNTB) was 14 (95% CI -9 to 3). We rated the quality of evidence as very low due to limitations in design, indirectness and imprecision <u>Participant-reported postoperative pain intensity measured with continuous scales</u> Two studies (104 participants, Akgul 2016; Martorella 2012) reported data on short-term effects of a psychological intervention on pain intensity measured with continuous scales (g 0.39, 95% CI -0.18 to 0.96) indicating no reduction of participant-reported postoperative pain in the psychological intervention group. We rated the quality of evidence as low due to limitations in indirectness and imprecision. Likewise, psychological interventions did not reduce pain intensity in the medium-term (g -0.02, 95% CI -0.24 to 0.20, I<sup>2</sup> = 34%, four studies, 413 participants). We rated the quality of evidence as moderate because of inconsistency. In line, longterm effects (g 0.05 95% CI -0.20 to 0.30, I<sup>2</sup> = 0%, two studies, 200 participants) did not show a reduction of pain intensity measured with continuous scales. Due to sparse data (imprecision), we rated the quality of evidence as moderate. Since we prespecified g 0.4 as a minimal clinically relevant group mean difference, the identified effect sizes cannot be regarded as clinically relevant.</p> <p>Author's Conclusion: In line with the conclusions of our previous review, there is a lack of evidence to support or refute psychological interventions in order to reduce postoperative pain in participants undergoing open heart surgery. We found moderate-quality evidence that psychological interventions reduced mental distress in participants undergoing open heart surgery. Given the small numbers of studies, it is not possible to draw robust conclusions on the efficacy of psychological interventions on outcomes such as analgesic use, mobility, and time to extubation respectively on adverse events or harms of psychological interventions.</p>
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**Methodical Notes**

Funding Sources: Internal sources  
• Leipzig University Hospital, Germany.  
External sources  
• Federal Ministry of Education and Research, Germany.  
Research funds (01KG1016)

COI: declared, see article.

**Study Quality:** Two review authors (SZ, SK) independently rated the quality of the evidence for each outcome. We used Review Manager to rank the quality of the evidence. We included a GRADE 'Summary of findings' table to present the main findings in a transparent and simple tabular format.

For main outcome : "We judged all of the other outcomes in this table to be low or very low quality."

For medium-term outcomes: "We judged all of the other outcomes in this table to be low or moderate quality."

**Heterogeneity:** Our review comprises substantial clinical diversity across studies in the intervention (contents, provider, dose, and duration) and outcome measures (e.g. various ways to assess mental distress or mobility). Consequently, tests of statistical heterogeneity indicated a large amount of heterogeneity in the analyses. However, subgroup analyses and sensitivity analyses could not explain the sources of heterogeneity.

Heterogeneity in main comparison is relatively low.

**Publication Bias:** "We did not find evidence of publication bias with regard to the secondary outcome mental distress measured in the medium-term and the long-term interval. Visually the funnel plots for the outcomes 'mental distress: medium-term' and 'mental distress: long-term' appeared not asymmetrical.

We used the test proposed by Egger et al (Egger 1997) to formally test funnel plot asymmetry and obtained no significant evidence of small-study effects (medium-term:  $P = 0.1256$ ; longterm:  $P = 0.0615$ ).

**Notes:**

Oxford level of evidence: 1 systematic review and meta-analysis.

**Schlüsselfrage:**

**3.3.1.2 Physiotherapie**

Fragestellung wird durch LL-Adaptation aktualisiert. Zusätzlich wurde in 2020 eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

**Inhalt: 6 Literaturstellen**

Literaturstelle	Evidenzlevel	Studientyp
Handoll, H. H. G. 2015	1	Systematic review and meta-analysis (31 studies in qualitative analysis, 8 in meta-analysis)
Handoll, H. H. G. 2011	1	Systematic review without meta-analysis due to differences in the trials.
Harvey, L. A. 2014	1	Systematic review and meta analysis (24 trials)
Nikolaidis, I. 2010	1	Systematic review and meta-analysis (2 studies)
Oosterhuis, T. 2014	1	Systematic review and meta-analysis (22 RCTS)
Smith, T. O. 2016	1	Systematic review and meta-analysis (3 studies)

**OXFORD (2011) Appraisal Sheet: Systematic Reviews: 6 Bewertung(en)**

Handoll, H. H. G. et al. Interventions for treating proximal humeral fractures in adults. Cochrane Database of Systematic Reviews. . . 2015			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (31 studies in qualitative analysis, 8 in meta-analysis)</p> <p>Databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process &amp; Other Non-Indexed Citations, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), AMED (Allied and Complementary Medicine), and PEDro - Physiotherapy Evidence Database.</p> <p>Search period: Inception - 10.2014</p> <p>Inclusion Criteria: We considered all randomised controlled trials (RCTs) and quasi-randomised controlled trials pertinent to the</p>	<p>Population: We included adults with a fracture of the proximal humerus. Stratification was planned by fracture type (e.g. based on the Neer classification or the AO classification) and by age (under versus over 65 years) if possible. Trials including children were included provided either separate data for skeletally mature participants were available or the proportion of children was small and, preferably, balanced in intervention groups.</p> <p>Intervention: Non-surgical and surgical interventions, as exemplified in Description of the intervention, used in the treatment and rehabilitation of fractures of the proximal humerus.</p> <p>Comparison: versus non-surgical treatment, comparison of different methods.</p>	<p>Primary:</p> <ul style="list-style-type: none"> <li>• Functional outcomes: patient-reported measures of upper-limb function (e.g. the Disability of the Arm, Shoulder, and Hand questionnaire (DASH), the Oxford Shoulder Score (OSS; Dawson 1996; Dawson 2009), and other validated shoulder rating scales).</li> <li>• Activities of daily living and health-related quality-of-life scores (e.g. EuroQol (EQ-5D); Short-Form 36 (SF-36) and Short-Form 12 (SF-12; Ware 1996).</li> <li>• Serious adverse events (e.g. death, deep infection, avascular necrosis, complex regional pain syndrome type 1) and need for substantive treatment, such as an operation.</li> </ul> <p>Secondary:</p> <ul style="list-style-type: none"> <li>• Composite scores of subjectively and objectively rated function and overall outcome (e.g. Constant and Murley's score (Constant 1987); Neer's rating (Neer 1970)).</li> <li>• Pain.</li> <li>• Upper limb strength and range of movement.</li> <li>• Less serious complications/adverse events of limited duration and impact (e.g. superficial infection, transient paraesthesia, skin irritation).</li> <li>• Patient satisfaction with treatment, including cosmetic outcomes.</li> <li>• Anatomical outcomes (e.g.</li> </ul>	<p>Agorastides 2007, Bertoft 1984, Boons 2012, Buecking 2014, Cai 2012, Fialka 2008, Fjalestad 2010, Hodgson 2003, Hoellen 1997, Kristiansen 1988, Kristiansen 1989, Lefevre-Colau 2007, Liversley 1992, Lopiz 2014, Lundberg 1979, Ockert 2010, Olerud 2011a,b ProFHER 2015, Revay 1992, Rommens 1993, Sebastia-Forcada 2014, Smejkal 2011, Soliman 2013, Stableforth 1984, Torrens 2012, Voigt 2011, Wirbel 1999, Zhang 2011, Zhu 2011, Zyto 1997.</p>

management of proximal humeral fractures in adults.

Exclusion Criteria: Pharmacological trials were excluded.

radiological deformity).

- Economic outcomes: each trial report was reviewed for cost and resource data, such as length of hospital stay and number of outpatient attendances, that would enable economic evaluation.

Results: Only summary shown here, due to length.

Summary:

9 trials evaluated non-surgical treatment in usually less severe fractures. One trial found a type of arm sling was generally more comfortable than a type of body bandage. There was some evidence that early mobilisation (within one week), compared with delayed mobilisation (after three weeks), resulted in less pain and faster recovery in people with 'stable' fractures. Two studies provided weak

evidence that many patients could generally achieve a satisfactory outcome when given sufficient instruction to pursue exercises on their own.

8 studies, involving 567 participants with displaced fractures, compared surgical versus non-surgical treatment. Pooled results from the five most recent trials showed that there were no important differences between the two approaches for patient-reported measures of function and quality of life at 6, 12 and 24 months. There was little difference between the two groups in mortality. Twice as many surgical group patients had additional or secondary surgery. More surgical group patients had adverse events.

12 trials (744 participants) tested different methods of surgical treatment. There was weak evidence of some differences (e.g. in complications) between some interventions (e.g. different devices or different ways of using devices). There was very limited evidence suggesting similar outcomes for early versus delayed mobilisation after either surgical fixation or hemiarthroplasty.

Author's Conclusion: Implications for practice

There is high or moderate quality evidence that, compared with non-surgical treatment, surgery does not result in a better outcome at one and two years after injury for people with displaced proximal humeral fractures involving the humeral neck and is likely to result in a greater need for subsequent surgery. The evidence does not cover the treatment of two-part tuberosity fractures, fractures in young people, high energy trauma, nor the less common fractures such as fracture dislocations and head splitting fractures.

There is insufficient evidence from randomised controlled trials to inform the choices between different



non-surgical interventions, different surgical interventions, or different rehabilitation interventions for these fractures.

## Methodical Notes

### Funding Sources: Internal sources

- University of Teesside, Middlesbrough, UK.

### External sources

- National Institute for Health Research, UK.

This project was supported by the National Institute for Health Research, via funding to the ProFHER trial (<http://www.nets.nihr.ac.uk/projects/hta/0640453>). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

COI: Helen Handoll is a member of the trial management group of ProFHER 2015; an independent review of this trial was performed by Stig Brorson. No other interests to declare. Stig Brorson was the lead investigator on Brorson 2009. No other interests to declare. Both authors performed independent study selection on the trial for which the other author was an investigator.

**Study Quality:** We used the tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

Most of the 31 studies had weaknesses that could affect the reliability of their results. We considered that the evidence was either of high or moderate quality for the results of the surgical versus non-surgical treatment comparison, which means that we are pretty certain these results are reliable. We considered that the evidence for other comparisons was of low or very low quality, which means we are unsure of these results.

**Heterogeneity:** We assessed heterogeneity for pooled data from comparable trials by visual inspection of the analyses along with consideration of the chi<sup>2</sup> test for heterogeneity and the IV statistic. The main quantitative assessment of heterogeneity was based on the IV statistic where the following interpretation from the Cochrane Handbook for Systematic Reviews of Interventions was used: 0%

to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity.

**Publication Bias:** There are insufficient data thus far (a minimum of 10 trials is required) to merit the production of funnel plots to explore publication bias.

### Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.

Handoll, H. H. G. et al. Interventions for improving mobility after hip fracture surgery in adults. Cochrane Database of Systematic Reviews. . . 2011

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review without meta-analysis due to differences in the trials.</p> <p>Databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, PEDro - The Physiotherapy Evidence Database.</p> <p>Search period: Last</p>	<p><b>Population:</b> Skeletally mature patients treated for a hip fracture at any stage during rehabilitation.</p> <p><b>Intervention:</b> Post-operative care programmes such as immediate or delayed weight bearing after surgery, and any other mobilisation strategies, such as exercises, physical training and muscle stimulation, used at various stages in rehabilitation, which aim to improve walking and minimise functional impairments. From this update (2010), trials testing mobilisation strategies with nutrition as a co-intervention are now included.</p> <p><b>Comparison:</b> other post-operative mobilisation techniques.</p>	<p><b>Primary:</b> 1. Mobility</p> <p>a. broad mobility measures (e.g. scales seeking to measure a number of aspects of mobility)</p> <p>b. walking</p> <p>i. self-reported measures</p> <p>ii. observed gait measures</p> <p>iii. use of walking aids/need for assistance</p> <p>c. balance while standing, reaching and stepping</p> <p>i. self-reported measures</p> <p>ii. observed balance measures</p> <p>2. Adverse eLects</p> <p>a. surgical complications of fixation within the follow-up period of the study</p> <p>i. reoperation</p> <p>ii. non-union of the fracture (the definition of non-union is that used within each individual study, and this outcome includes early re-displacement of the fracture)</p> <p>iii. avascular necrosis</p> <p>iv. other complications (e.g. thromboembolic complications (deep vein thrombosis or pulmonary embolism))</p> <p>b. readmission</p> <p>c. mortality</p> <p>d. pain (persistent pain at the final follow-up assessment)</p> <p>e. falls</p> <p><b>Secondary:</b> Secondary outcomes</p> <p>1. General functioning</p> <p>a. return to living at home</p> <p>b. health related quality of life measures</p>	<p>Baker 1991, Binder 2004, Braid 2008, Gorodeskyi 2007, Graham 1968, Hauer 2002, Karumo 1977, Lamb 2002, Lauridsen 2002, Mangione 2005, Miller 2006, Mitchell 2001, Moseley 2009, Oldmeadow 2006, Resnick 2007, Sherrington 1997, Sherrington 2003, Sherrington 2004, Tsauo 2005.</p>

version -04 / 2010

**Inclusion Criteria:** All randomised or quasi-randomised trials comparing different mobilisation strategies after hip fracture surgery.

**Exclusion Criteria:** Trials testing interventions started after the generally perceived recovery of around one year were excluded. Excluded were trials testing interventions that did not aim specifically to improve mobility, and those testing care programmes, management strategies and other multi-component interventions that were not solely aimed at mobilisation.

2. Muscle strength
3. Patient satisfaction
  - a. acceptability of interventions
  - b. adherence
4. Resources
  - a. length of hospital stay (in days)
  - b. number of physiotherapy sessions
  - c. number of outpatient attendances
  - d. need for special care

**Results: Study population:**

All 19 included trials were published as full reports in journals, from 1968 to 2009. 18 were RCTs, although two of provided no details of their method of randomisation and thus use of quasi-randomised methods for sequence generation cannot be ruled out.

The 19 included trials involved a total of 1589 patients. Studysize ranged from 26 participants to 273 participants.

The majority of participants in each trial were women (67% to 100% of trial population). 5 trials only included women. The mean ages of trial participants ranged from 71 years to 84 years; and was 80 or above in 11 trials. Thirteen trials set lower age limits, ranging from 50 years to 75 years.

**Results:**

No data pooling was performed given the differences in the trials, primarily in their interventions and settings.

Only summary described here due to length, for individual results see article.

**Intervention soon after surgery:**

12 trials evaluated interventions started soon after hip fracture surgery. Single trials found improved mobility from, respectively, a two-week weight-bearing programme, a quadriceps muscle strengthening exercise programme and electrical stimulation aimed at alleviating pain. Single trials found no significant improvement in mobility from, respectively, a treadmill gait retraining programme, 12 weeks of resistance training, and 16 weeks of weight-bearing exercise.

One trial testing ambulation started within 48 hours of surgery found contradictory results. One historic trial found no significant difference in unfavourable outcomes for weight bearing started at two versus 12 weeks. Of two trials evaluating more intensive physiotherapy regimens, one found no difference in recovery, the other reported a higher level of drop-out in the more intensive group. Two trials tested electrical stimulation of the quadriceps: one found no benefit and poor tolerance of the intervention; the other found improved mobility and good tolerance.

**Intervention after hospital discharge:**

Seven trials evaluated interventions started after hospital discharge. Started soon after discharge, two trials found improved outcome after 12 weeks of intensive physical training and a home-based physical therapy programme respectively. Begun after completion of standard physical therapy, one trial found improved outcome after six months of intensive physical training, one trial found increased activity levels from a one year exercise programme, and one trial found no significant effects of home-based resistance or aerobic training. One trial found improved outcome after home-based exercises started around 22 weeks from injury. One trial found home-based weight-bearing exercises starting at seven months produced no significant improvement in mobility.

**Author's Conclusion: Implications for practice**

There is insufficient evidence from randomised trials to determine the effects of any particular mobilisation strategy or programme started either in the early or later rehabilitation period after hip fracture surgery. However, the included trials generally indicate that it is possible to enhance mobility after hip fracture though the optimal method to achieve this remains unclear.

	<p>While the most successful programmes evaluated to date have involved intensive supervised ongoing exercise, the optimal format and resource implications for these strategies are not established.</p> <p>Clearly, intervention is required to restore and enhance mobilisation in older people after surgery for hip fracture. The interventions chosen should match the needs of individual patients and be based on agreed local practice guidelines. Such guidelines, which should acknowledge and allow for the insufficiency of the underlying evidence to inform practice, should also include consideration of the continued risk of further falls and fractures and potential for functional decline in this often frail patient population.</p>	
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<b>Methodical Notes</b>	<p><b>Funding Sources:</b> Internal sources</p> <ul style="list-style-type: none"> <li>• University of Teesside, Middlesbrough, UK.</li> <li>• School of Physiotherapy, University of Sydney, Australia.</li> </ul> <p>External sources</p> <ul style="list-style-type: none"> <li>• National Health and Medical Research Council, Fellowship, Australia.</li> </ul> <p><b>COI:</b> None known. However, as Catherine Sherrington is an active investigator in several randomised trials in this area, assessment of eligibility of these trials and quality assessment of the four included trials was done independently by two others. Independent data extraction and entry into RevMan, presentation and interpretation of these four trials were also performed.</p> <p><b>Study Quality:</b> Risk of bias was independently assessed, without masking of the source and authorship of the trial reports, by at least two authors for newly included trials, and by at least one author for trials that had been assessed in previous versions of the review. The assessment form was piloted using two trials. Between rater and between versions consistency in assessment was checked by HH at data entry. All differences were resolved by discussion. We used the tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions.</p> <p>"There is a strong possibility of biased results resulting from methodological weaknesses of several trials. 13 trials were judged at high risk of bias on at least one aspect, more frequently a lack of blinding."</p> <p><b>Heterogeneity:</b> We planned to assess heterogeneity by visual inspection of the forest plot (analysis) along with consideration of the chi2 test for heterogeneity and the I2 statistic.</p> <p>In the absence of data to enable meta-analysis, subgroup analyses were also not possible. Planned subgroup analyses were by gender, prefracture mobility, cognitive impairment, and for early mobilisation, type of fracture (intracapsular versus extracapsular fractures).</p> <p><b>Publication Bias:</b> There were insufficient trials and data for the assessment of reporting biases. Our search of clinical trial registers has the potential to reduce the impact of publication bias, especially in the future. For individual trials, we checked all publications and trial registration details where available to assess consistency in outcome reporting.</p> <p><b>Notes:</b></p> <p>Oxford level of evidence: 1 Systematic review and meta-analysis.</p> <p>Notes: No data was pooled due to differences in the trials, therefore this article can be considered a systematic review.</p>
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<p>Harvey, L. A. et al. Continuous passive motion following total knee arthroplasty in people with arthritis. Cochrane Database of Systematic Reviews. . . 2014</p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta analysis (24 trials)</p> <p>Databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 12); MEDLINE</p>	<p>Population: Participants could be of any age provided they were hospitalised following Total knee arthroplasties (TKA). All participants needed to have a pre-surgery diagnosis of arthritis.</p> <p>Intervention: Continuous passive motion (CPM) and standard postoperative care.</p> <p>Standard postoperative care could include muscle-strengthening exercises (isometric or dynamic), functional exercises, gait training, immobilisation or ice, provided both groups received the same intervention.</p> <p>Additional knee exercises</p>	<p>Primary:</p> <ul style="list-style-type: none"> <li>• Active knee flexion ROM,</li> <li>• pain (Only direct measures of pain intensity were of interest. These included pain scales but not pain medication.)</li> <li>• function,</li> <li>• quality of life,</li> <li>• participants' global assessment of treatment effectiveness,</li> <li>• need for manipulation under anaesthesia</li> <li>• adverse events.</li> </ul> <p>Secondary:</p> <ul style="list-style-type: none"> <li>• passive knee flexion ROM,</li> <li>• active knee extension ROM,</li> <li>• passive knee extension ROM,</li> <li>• length of hospital stay,</li> <li>• swelling</li> <li>• quadriceps strength.</li> </ul> <p>Results: Only pain and adverse events outcomes reported here, due to length. Rest see</p>	<p>Alkire 2010, Bennett 2005, Bruun-Olsen 2009, Can 1995, Chiarello 1997, Colwell 1992, Denis 2006, Harms 1991, Huang 2003, Kumar 1996, Lau 2001, Lenssen 2003a, Lenssen 2008, MacDonald 2000, Maniar 2012, May 1999, McInnes 1992, Montgomery 1996, Ng 1999, Nielsen 1988, Ritter 1989, Sahin 2006, Vince 1987, Worland 1998.</p>

<p>(January 1966 to January 24, 2013);</p> <ul style="list-style-type: none"> <li>• EMBASE (January 1980 to January 24, 2013);</li> <li>• CINAHL (January 1982 to January 24, 2013);</li> <li>• AMED (January 1985 to January 24, 2013);</li> <li>• PEDro (to January 24, 2013).</li> </ul> <p>Search period: Inception - 2012</p> <p>Inclusion Criteria: Only randomised controlled trials (RCT), regardless of language. We accepted abstracts. We did not exclude trials based on quality assessment.</p> <p>Exclusion Criteria: -</p>	<p>could include instructions or supervised active or passive knee ROM exercises. They could not include knee exercises provided with any type of CPM device.</p> <p>Comparison: Similar postoperative care with or without additional knee exercises.</p>	<p>article.</p> <p>Primary results:</p> <p>2. Pain</p> <p>Level of evidence was considered to be low.</p> <p><u>Short-term effects:</u> 11 trials with 683 participants measured pain. 8 trials with 414 participants provided useful data. Pain was measured on a 10- or 100-point visual analogue scale but we converted all results to a 10-point scale for this review. The MD was -0.4 points on a 0- to 10-point scale with less pain for the CPM group (95% CI -0.8 to 0.1; P value = 0.1; I<sup>2</sup> = 50%).</p> <p><u>Medium-term effects:</u> 4 trials with 243 participants measured pain. 3 trials with 179 participants provided useful data. Pain was measured on a 10- or 100-point visual analogue scale but we converted all results to a 10-point scale for this review. The MD was 0.3 points on a 0- to 10-point scale with more pain for the CPM group (95% CI -0.4 to 0.9; P value = 0.44; I<sup>2</sup> = 52%).</p> <p><u>Long-term effects:</u> One trial with 28 participants measured pain using a 10-point visual analogue scale (Sahin 2006). The MD was 0.1 points on a 0- to 10-point scale with more pain for the CPM group (95% CI -0.8 to 0.9; P value = 0.87).</p> <p>7. Adverse events</p> <p>17 trials with 1104 participants reported incidence proportion of adverse events. 16 trials with 1040 participants provided useful data. Level of evidence was considered to be low.</p> <p>Adverse events included delayed healing, haemarthrosis, falls, deep venous thromboses, wound infections, pulmonary emboli, knee haematoma and a patellar rupture. There were 178 adverse events in total. The RR was 0.92 with less risk for the CPM group (95% CI 0.63 to 1.33; P value = 0.65; I<sup>2</sup> = 39%).</p> <p>Author's Conclusion: Implications for practice The effects of continuous passive motion (CPM) on range of motion (ROM), pain, function and quality of life are too small to justify its use and costs but the effects of CPM on participants' global assessment of treatment effectiveness are unclear. This review provides very low-quality evidence that CPM reduces the risk of manipulation under anaesthesia; however, these findings need to be interpreted with caution because they are inconsistent with the moderate-quality evidence indicating that CPM has no effect on knee ROM even though the main indication for manipulation under anaesthesia is joint stiffness.</p>	
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<p><b>Methodical Notes</b></p> <p>Funding Sources: Internal sources</p> <ul style="list-style-type: none"> <li>• The University of Ottawa, Canada.</li> <li>• The Rehabilitation Studies Unit, Sydney School of Medicine/Northern, University of Sydney, Australia, Other.</li> </ul> <p>External sources</p> <ul style="list-style-type: none"> <li>• NHMRC, Australia. fellowship for RDH</li> </ul> <p>COI: None known.</p> <p>Study Quality: We used the GRADE approach to summarise the quality of evidence about the effect of CPM on each of the primary outcomes.</p> <p>Heterogeneity: We planned no sensitivity analyses; however, we did look for small sample bias by re-doing all the analyses using a fixed-effect model and comparing results between the random-effects model and fixed-effect model of analyses for each outcome</p> <p>Publication Bias: not investigated.</p> <p>Notes:</p> <p>Oxford level of evidence: 1 Systematic review and meta-analysis</p> <p>No investigation of publication bias. No definition how the authors interpret heterogeneity.</p>
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Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
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<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (2 studies)</p> <p>Databases: CENTRAL, MEDLINE, and EMBASE to 1998 for the original review. A revised search was run in CENTRAL (The Cochrane Library 2008, Issue 2), MEDLINE, and EMBASE, and CINAHL (January 1998 to June 2008) to update the review.</p> <p>Search period: Last version - 2008</p> <p>Inclusion Criteria: All randomised or quasi-randomised controlled trials allocating patients with cervical radiculopathy or myelopathy to 1) "medical management" or "decompressive surgery (with or without fusion) plus medical management" 2) "early decompressive surgery" or "delayed decompressive surgery."</p> <p>Exclusion Criteria: not specified.</p>	<p>Population: Patients with a clinical diagnosis of cervical radiculopathy (pain along the cutaneous distribution of one or more cervical roots, sometimes associated with weakness and hyporeflexia), or myelopathy (spasticity and weakness in the lower limbs with or without "numb and clumsy" hands), and supported by appropriate radiological findings.</p> <p>Intervention: Any form of surgical decompression in the cervical spine, with or without fusion, designed to alleviate the symptomatic cord or root compression.</p> <p>Comparison: conservative treatment</p>	<p>Primary: i) Surgical morbidity (neurological deficit, oesophageal or recurrent laryngeal nerve injury, deep seated infection or repeat surgery) and mortality (within four weeks of surgery)</p> <p>ii) Pain intensity (in the neck, head or limbs) measured by: visual analogue scale, or other measure of pain severity.</p> <p>iii) Functional performance of the arms or legs measured by: nine-hole peg task, 10-metre walk, NCSS, Sickness Impact Profile, Odom's and Ranawat's criteria, Nurick's scale (Nurick 1972).</p> <p>iv) Mood measured by: Mood Adjective Check List and Hospital Anxiety and Depression (HAD) scale, or other validated questionnaire.</p> <p>v) Quality of life measured by: SF-36, Health Assessment Questionnaire (HAQ) or EuroQol.</p> <p>Secondary: not described.</p> <p>Results: Description of studies 2 studies were included in the review. One trial recruited 81 patients with cervical radiculopathy (Persson 1997). One trial recruited 68 patients with cervical myelopathy Bednarik 1999.</p> <p>Effects of interventions Only morbidity and pain reported here, due to length, other outcomes see article.</p> <p><u>A) Surgical morbidity or mortality-number of procedures per patient</u> No major adverse events or deaths related to surgery were reported in the trials. In Persson 1997, one surgically-treated patient had a graft infection and was operated on again (between three months and one year from the time of the original enrolment). Another surgically-treated patient had an exploration of the brachial plexus and a further six patients had surgery in adjacent levels during the same period. In Kadanka 2002, five patients died, at least two years from the time of the initial enrolment.</p> <p><u>B) RADICULAR PAIN in cervical radiculopathy.</u> One trial included randomised data from 81 patients and evaluated radicular pain in cervical radiculopathy (Persson 1997). The pain intensity was assessed by means of a visual analogue scale (VAS). Current pain and worst pain during the preceding week was reported. This was repeated eight to 12 days later and the mean value was used for statistical analysis. There is low quality evidence (unable to generalize, sparse data) from one trial (N = 81), that at three months, surgically treated patients had significantly less pain than those treated with physiotherapy (MD -14, 95% CI -27.84 to -0.16) and a cervical collar (MD -21, 95% CI -33.32 to -8.68), but at one year, there was no statistical difference between the groups (Physio: MD -9, 95% CI -23.39 to 5.39; Collar:(MD -5, 95% CI -18.84 to 8.84)). There was also low quality evidence (unable to generalize, sparse data) from one trial (N = 81), that at three months, the 'worst pain in the preceding week' reported by surgically-treated patients was significantly less than those treated with a collar at three months ((MD -21, 95% CI -36.89 to -5.11), but there were no significant differences between the groups at one year (MD -10, 95% CI -30.79 to 10.79).</p> <p>Author's Conclusion: Implications for practice The available small randomised trials do not provide reliable evidence on the effects of surgery for cervical spondylotic radiculopathy or myelopathy. There is low quality evidence from one trial (81 patients) that surgery appears to provide pain relief faster in patients who suffer with cervical radiculopathy, compared to physiotherapy or hard collar immobilization. There is low quality evidence from the same trial that the long term effectiveness of physiotherapy or hard collar immobilization is possibly equally effective. There is very low quality evidence from one trial (68 patients) that patients with mild myelopathy feel subjectively better following surgery, but there was no evidence from objective testing of any benefit for up to three years. It is not clear whether the short-term risks of surgery are offset by any long-term benefits.</p>	<p>Kadanka 2002, Persson 1997,</p>
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Funding Sources: not described.

COI: None Known.

**Study Quality:** The quality of evidence for each outcome was assessed using the GRADE approach (Furlan 2009). Each outcome was assessed on five domains: limitation of study design, inconsistency, indirectness (inability to generalize), imprecision (insufficient or imprecise data) of results, and publication bias. The overall quality of evidence for each outcome is the result of the combination of the assessments in all domains.

"Both studies were small and therefore prone to small study bias. Issues related to selection bias, performance bias, attrition bias and detection bias (in both trials, inherent to studies including surgically-treated patients) were identified.

**Heterogeneity:** "Sensitivity analyses were to be performed on the basis of methodological quality and to test for heterogeneity in the results."

No tests for heterogeneity were performed, since the two studies were not pooled.

**Publication Bias:** Not investigated or possible, since there are only two studies, that have been included.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Only two studies were included in the article, therefore the implications might be limited.

Oosterhuis, T. et al. Rehabilitation after lumbar disc surgery. Cochrane Database of Systematic Reviews. . . 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (22 RCTS)</p> <p>Databases: CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO and PEDro</p> <p>Search period: Inception - 06.2013</p> <p>Inclusion Criteria: Randomised controlled trials (RCTs), active rehabilitation after lumbar disc surgery vs not treatment regarding pain, efficacy, improvement of condition.</p> <p>Exclusion Criteria: Nonrandomised controlled trials (CCTs) or quasi-RCTs were excluded.</p>	<p><b>Population:</b> Participants aged between 18 and 65 years who had first-time lumbar disc surgery because of a lumbar disc prolapse were included. All types of surgical techniques for lumbar disc herniation (e.g. standard discectomy, microdiscectomy, laser discectomy, chemonucleolysis) were included.</p> <p><b>Intervention:</b> Active rehabilitation programmes after lumbar disc surgery include exercise therapy, strength and mobility training, physiotherapy and multidisciplinary programmes, which may include elements of back schools and ergonomics aiming at, for example, motor control modification, resumption of activities of daily living including work and physical activity and enhancement of pain coping strategies. These programmes may consist of individual sessions, group training or education or a combination of these.</p> <p><b>Comparison:</b> no treatment or other modality of active rehabilitation.</p>	<p><b>Primary:</b> Pain (e.g. visual analogue scale (VAS)), a global measure of improvement (overall improvement, proportion of participants recovered, subjective improvement of symptoms), back pain-specific functional status (e.g. Roland-Morris Disability Questionnaire (RDQ), Oswestry Disability Index (ODI)) and return to work (return-to-work status, days of work).</p> <p><b>Secondary:</b> Outcomes of physical examination (e.g. spinal range of motion, straight-leg raise range of motion, muscle strength), behavioural outcomes (e.g. anxiety, depression, pain behaviour) and generic functional status (Short Form (SF)-36, Nottingham Health Profile, Sickness Impact Profile)</p> <p>Other outcomes such as medication use, reherniation, reoperation and adverse effects were also considered.</p> <p><b>Results:</b> Only immediate postoperative rehabilitation programmes reported in this section, due to length (rest see article)</p> <p>1. Comparisons among rehabilitation programmes that start immediately after surgery</p> <p><u>1a. Treatment versus no treatment, placebo or waiting list control</u></p> <p>Very low-quality evidence, based on one very small (N = 14) RCT with a high risk of bias (Ju 2012), suggests that there is no difference in pain posttreatment (12 weeks postoperative) between an exercise programme and no rehabilitation. The intervention group had significantly lower scores than the control group for function post-treatment (mean difference -3.99; 95% (CI) -4.95 to -3.03; Analysis 1.2).</p> <p><u>1b. Treatment versus other kinds of treatment</u></p> <p>Very low-quality evidence, based on one small (N = 60) RCT with a high risk of bias (Kjellby-Wendt 1998), suggests that there</p>	<p>Alaranta 1986, Choi 2005, Danielsen 2000, Dolan 2000, Donaldson 2006, Donceel 1999, Erdogmus 2007, Filiz 2005, Hakkinen 2005, Johanssen 1994, Johansson 2009, Ju 2012, Kjellby-Wendt 1998, Kulig 2009, Manniche 1993a, Manniche 1993b, McGregor 2011, Newsome 2009, Ostelo 2003, Scrimshaw 2001, Timm 1994, Yilmaz 2003,</p>

is no difference over the long term in global perceived effect, pain or return to work between an intensive exercise programme and a less active programme. Very low-quality evidence, based on one very small RCT (N = 30) with a high risk of bias (Newsome 2009), shows that immediate physiotherapy, starting two hours postsurgery (consisting of 10 times flexion of knee and hip and the advice to repeat this every 30 minutes), and usual care do not significantly differ at four weeks and three months in terms of function, back pain (Analysis 3.3; Analysis 3.4), leg pain and McGill pain scores. The intervention group returned to work earlier (median six weeks vs control eight weeks) (median difference two weeks, 95% (CI) zero to six). In each group, one recurrent disc protrusion was reported; data on reoperations were not presented.

**1c. Specific intervention in addition to a treatment programme versus treatment alone**

Low-quality evidence from one RCT (N = 59) (Scrimshaw 2001) with a low risk of bias shows that neural mobilisation is not effective as an adjunct to standard postoperative care in terms of functional status and pain after six weeks of followup. For these outcome measures, as well as for overall improvement, no differences were noted after 12 months. No data on reoperation rates were presented.

**Author's Conclusion: Implications for practice**

In clinical practice, considerable variation is seen in the content, duration and intensity of rehabilitation programmes. Based on this review, because of lack of high- or moderate-quality evidence, no firm conclusion can be drawn regarding their effectiveness, and consequently, no strong recommendations can be made for clinical practice. Taking this caution into account, it seems that exercise programmes starting four to six weeks postsurgery lead to a faster decrease in pain and disability than no treatment, and that highintensity exercise programmes lead to a slightly faster decrease in pain and disability than low-intensity programmes. No evidence suggests that these active programmes increase the reoperation rate or that patients need to have their activities restricted after first-time lumbar disc surgery.

**Methodical Notes**

**Funding Sources:** none declared.

**COI:** Raymond Ostelo, Riekie de Vet and Chris Maher, authors of this second update of the review, were authors of one of the included studies.

As this is a potential conflict of interest, they were not involved in the methodological quality assessment, in data extraction or in any other decision regarding these trials.

**Study Quality:** The risk of bias of the included studies was assessed by using the criteria recommended in the updated method guidelines of the Cochrane Back Review Group.

About half of the included studies (10 out of 22) had a low risk of bias.

**Heterogeneity:** Assessment of heterogeneity was based on I<sup>2</sup> tests. Results were combined in a meta-analysis if I<sup>2</sup> < 50%. If I<sup>2</sup> > 50%, we assessed how serious heterogeneity was by inspecting the forest plots. If the heterogeneity was thought not to be too serious, a random-effects model was used to pool the data, to take heterogeneity into account. If substantial statistical or clinical heterogeneity (study population, types of treatments, outcomes and measurement instruments) was present, the results were not combined but were presented by a narrative synthesis and description of characteristics in the table showing the studies included.

Publication Bias: No known or suspected publication bias was detected.

Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis

Notes: Unclear definition of inclusion and exclusion criteria.

Smith, T. O. et al. Assistive devices, hip precautions, environmental modifications and training to prevent dislocation and improve function after hip arthroplasty. Cochrane Database of Systematic Reviews. . . 2016

Evidence Types	level/Study	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (3 studies)</p> <p>Databases: MEDLINE, EMBASE, the Cochrane Library including CENTRAL, Database of Reviews of Effects (DARE), Health Technology Assessment (HTA), Economic Evaluations Database (EED), CINAHL, PEDro and CIRRIE.</p> <p>In addition we checked Controlled Clinical Trials, Clinicaltrials.gov, the National Institutes of Health Trial Registry, theWorld Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the OpenGrey database.</p> <p>Search period: Inception - 04.2016</p> <p>Inclusion Criteria: We included randomised controlled trials (RCTs), quasi-RCTs and cluster-RCTs that evaluated the effectiveness of the provision of assistive devices, education on hip precautions, environmental modifications, or training in ADL and EADL for people undergoing THA. The main outcomes of interest were pain, function, health-related quality of life (HRQOL), global assessment of treatment success, reoperation rate, hip dislocation and adverse events.</p> <p>Exclusion Criteria: "We excluded non-RCTs. If we could not isolate the nature of the occupational therapy intervention, or it formed less than 75% of the overall intervention package, we excluded the study."</p>	<p>Population: "Participants who underwent primary THA surgery for osteoarthritis or revision THA. If we had excluded studies that included a few participants who received a THA for reasons other than osteoarthritis, this may have limited the information available for inclusion in this review. Therefore, we included studies if most participants (over 80%) who underwent THA surgery for osteoarthritis. We included trials that included various pathologies and various orthopaedic surgeries (that is total knee arthroplasty, hip resurfacing, hemi-arthroplasty) if the study authors presented results for THA for osteoarthritis. We considered all types of prostheses, fixation methods and surgical approaches for inclusion."</p> <p>Intervention: • Provision of and education about using assistive devices for preventing dislocation. (raised toilet seats, furniture raises, dressing aids, perching stools, longhanded grabbers and commodes).</p> <p>• Postoperative education about hip precautions and specifically on teaching joint positions associated with joint dislocation (hip flexion beyond 90°, adduction beyond the midline, and to avoid internal and external rotation beyond 20° from neutral).</p> <p>• Environmental modifications such as: removal of trip hazards; amended layout of furniture to improve access around the home; amended layout of specific rooms such as bathrooms, the kitchen and bedroom; and installation of handrails or grab rails.</p> <p>• Assessment, facilitation, practice and re-assessment of selfcare activities of daily living (ADL) tasks to foster independence and skills in these activities.</p> <p>• Training of extended ADL (EADL) or (also known as) instrumental ADL (IADL) as these skills are aimed at improving health-related quality of life (HRQOL). This may have included specific training to facilitate activities beyond personal or selfcare ADL and may therefore have included activities such as gardening, shopping and social pursuits.</p> <p>• Provision of specific advice about coping strategies to manage pain and activity pacing.</p> <p>• Postoperative education sessions designed to inform participants of their expected pathway from the</p>	<p>Primary: • Pain as measured with tools such as a visual analogue or rating scale, or formal tools such as the McGill Pain Questionnaire.</p> <p>• Function, as measured by WOMAC function; Oxford Hip Score; Harris Hip Score ; Short Form (SF)-36 Physical Component Score; SF-12; Health Assessment Questionnaire; Objective Functional Capability Index (OFCI) and Subjective Functional Capability Index (SFCI).</p> <p>• HRQOL (e.g. SF-36, SF-12, Frenchay Activities Index, EuroQoL, Nottingham Health Profile (NHP)).</p> <p>• Global assessment of treatment success.</p> <p>• Hip dislocation, as reported (e.g. the number of participants requiring a manipulation under anaesthetic to reduce a dislocated hip prosthesis, or the requirement of a revision procedure due to recurrent hip dislocation).</p> <p>• Reoperation rate.</p> <p>• Total adverse events (e.g. infection, thrombosis, falls).</p> <p>Secondary: • Limitations in personal ADL during the initial six weeks, which are defined as the basic activities that everyone undertakes to maintain a personal level of care (e.g. feeding, toileting, washing, bathing, transfer in and out of bed or on/off a chair, mobilising). Personal ADL may be assessed using instruments such as the Barthel Score or Iowla Level of Assistance Score.</p> <p>• Restrictions in performance in extended ADL (EADL) or instrumental ADL (IADL), which are defined as the skills required to live independently and manage a dwelling (e.g. preparing own meals, doing housework, managing own money, shopping). This may be assessed using instruments such as the Oxford Hip Score or the Nottingham extended ADL scale.</p> <p>• Societal reintegration or discretionary activities. These are the higher function activities such as driving, using local services, using public transport, socialising with friends, attending social or cultural events. This outcome measure differs from HRQOL measures since this outcome specifically relates to social interaction and participation activities rather than more generic ADL, which are captured through the HRQOL outcomes.</p> <p>• Length of hospital stay following THA.</p> <p>• Cost-analysis. This includes specific occupational therapy costs, overall rehabilitation costs, or overall hospital costs.</p> <p>Results: 3 included trials randomised a total of 492 participants (530 THAs). This consisted of 287 participants who received</p>	<p>Peak 2005, Ververeli 2009, Wong 1990</p>	



operative procedure to recovery at home to reduce anxiety and improve preparation for hospital discharge, and specific advice on how to access other services for support following THA (e.g. access to other professional services).

Comparison: • Rehabilitation therapy excluding the interventions of interest (assistive devices, hip precautions, environmental modifications).

- No rehabilitation therapy provided.
- One intervention of interest versus another.

an 'experimental' rehabilitation approach following THA and 242 participants who received a control or 'usual treatment' approach following THA.

Only summary results displayed, due to length, rest see article.

Summary of results:

One study (81 participants) compared outcomes for participants randomised to the provision of hip precautions, equipment and functional restrictions versus no provision of hip precautions, equipment or functional restrictions. Due to the quality of evidence being very low, we are uncertain if the provision of hip precautions, equipment and functional restrictions improved function measured using the Harris Hip Score at 12 month follow-up, or health-related quality of life (HRQOL) measured by the Short Form-12 at four week follow-up, compared to not providing this. There were no incidences of hip dislocation or adverse events in either group during the initial 12 postoperative months. The study did not measure pain score, global assessment of treatment success or total adverse events.

One study (265 participants; 303THAs) evaluated the provision of hip precautions with versus without the prescription of postoperative equipment and restrictions to functional activities. Due to the quality of evidence being very low, we are uncertain if perceived satisfaction in the rate of recovery differed in people who were not prescribed postoperative equipment and restrictions (135/151 satisfied) compared to those prescribed equipment and restrictions (113/152) (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.75 to 0.93; 265 participants, one trial; number needed to treat for an additional beneficial outcome (NNTB) = 7). Due to the low quality evidence, we are uncertain if the incidence of hip dislocation differed between participants provided with hip precautions with (1/152) compared to without providing equipment or restrictions post-THA (0/151) (RR 2.98, 95% CI 0.12 to 72.59). The study did not measure pain, function, HRQOL, re-operation rates or total adverse events.

One study (146 participants) investigated the provision of an enhanced postoperative education and rehabilitation service on hospital discharge to promote functional ADL versus a conventional rehabilitation intervention in the community. This study was of very low quality evidence. We were uncertain if the provision of enhanced postoperative education and rehabilitation improved function at six months follow-up, when assessed using the Objective and Subjective Functional Capability Index (146 participants, one trial; P >0.05; no numerical results provided) compared to conventional rehabilitation. The study did not measure pain score, HRQOL, global assessment of treatment success, hip dislocation, re-operation rate or total adverse events.

Author's Conclusion: Implications for practice

It is uncertain if the prescription of postoperative equipment and placing

functional limitations on patients following primary antero- lateral THA is beneficial due to the very low quality evidence available from three single studies. It is uncertain whether the provision of functional limitations and postoperative equipment is beneficial for functional recovery and societal reintegration of patients following THA due to the very low quality evidence available.

There is insufficient evidence to provide any recommendations on whether hip precautions (limiting hip flexion, adduction or rotation) are required in the initial six postoperative weeks following THA. From the single study of very low quality evidence (Peak 2005), it is uncertain whether there is a difference in complication rates such as hip dislocation, but modifying this advice has yet to be assessed in isolation, having only been assessed with the addition of equipment and functional restrictions.

Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, we judged the quality of the evidence as 'very low', and downgraded the quality of the evidence due to limitations in design and implementation and for imprecision. There is insufficient evidence to support or refute the adoption of an enhanced postoperative intervention and community rehabilitation consisting of functional reintegration and education compared to conventional rehabilitation strategies.

The single study that investigated this was underpowered, poorly reported and we judged it as at high risk of bias.

#### Methodical Notes

##### Funding Sources: Internal sources

- No sources of support supplied

##### External sources

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

The funding for this review is from the NIHR programme grant 'improving patients' experience and outcome of total joint replacement' (RP-PG-0407-10070)

- West Midlands Strategic Health Authority (WMSHA), UK.

The main review author (PJ) is in receipt of a WMSHA Nursing, Midwifery and Allied health professionals Pre-PhD training award

COI: No known conflicts of interest.

**Study Quality:** We used the Cochrane 'Risk of bias' tool (Higgins 2011) to assess the quality of the included studies. We assessed the following domains.

The three included studies, which were at moderate to high risk of bias.

**Heterogeneity:** We planned to assess all studies we judged to be homogeneous for the potential statistical variability of the treatment effects due to heterogeneity via calculation of the  $I^2$  statistic. This measure describes the percentage total variation across studies that results from heterogeneity rather than chance. We used the following guidelines for interpretation (Deeks 2011): 0% to 40% may be unimportant; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity.

"All included studies were heterogenous for the interventions under investigation."

**Publication Bias:** Due to the limited number of eligible papers we identified by the search strategy, we were unable to: construct a funnel plot to assess small sample size publication bias; perform a meta-analysis to pool the data from the included studies; or undertake subgroup or sensitivity analyses for pooled data.

##### Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.

No meta-analysis was performed in the traditional sense, since the three included studies investigated different interventions. The three included studies were at moderate to high risk of bias.

Therefore the presented article might be of limited use.



Schlüsselfrage:

3.3.1.3 Kältetherapie

Fragestellung wird durch LL-Adaptation aktualisiert. Zusätzlich wurde in 2020 eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

Inhalt: 2 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Adie, S. 2012	1	Systematic review and meta-analysis
East, C. E. 2012	1	Systematic review and meta-analysis.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Adie, S. et al. Cryotherapy following total knee replacement. Cochrane Database of Systematic Reviews. . . 2012			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis</p> <p>Databases: Cochrane Database of Systematic Reviews, CENTRAL, DARE, HTA Database, MEDLINE, EMBASE, CINAHL, PEDro and Web of Science</p> <p>Search period: Inception - 15th March 2012.</p> <p>Inclusion Criteria: Randomised controlled trials or controlled clinical trials in which the experimental group received any form of cryotherapy, and was compared to any control group following TKR indicated for osteoarthritis.</p> <p>Exclusion Criteria: not specified, (not meeting inclusion)</p>	<p>Population: Patients with patients undergoing total knee replacement (TKR).</p> <p>Settings: Post-operative</p> <p>Intervention: Any cold therapy</p> <p>Comparison: Any control</p>	<p>Primary: blood loss, post-operative pain, adverse events, range of motion discharge, transfusion rate</p> <p>Secondary: -</p> <p>Results: Pain</p> <p>7 studies measured pain at different time points. Outcomes were pooled on a 10 point VAS scale, with negative scores indicating a beneficial elect for the cryotherapy group.</p> <p>POD 1: 6 studies with 500 patients measured pain at POD 1 (Analysis 1.14). The MD was -0.22 points (95% CI -0.93 to 0.49; P = 0.55; I2 = 40%).</p> <p>POD 2: 4 studies with 322 patients measured pain at POD 2 (Analysis 1.9). The MD was -1.32 points (95% CI -2.37 to -0.27; P = 0.01; I2 = 54%), indicating less pain in those with cryotherapy.</p> <p>POD 3: 6 studies with 431 patients measured pain at POD 3 (Analysis 1.10). The MD was -0.47 points (95% CI -1.40 to 0.47; P = 0.85; I2 = 78%).</p> <p>"While there was a statistically significant benefit of cryotherapy for pain at 48 hours, this was not seen at 24 or 72 hours."</p> <p>Adverse Effects</p> <p>Eleven studies with a total of 707 patients measured the occurrence of adverse events however, data from only five studies was pooled due to studies with zero events. The most commonly reported adverse event was withdrawal due to cold discomfort. Apart from Levy 1993, which reported two events of deep venous thrombosis (one intervention and one control), no serious adverse elects were reported. The RR for adverse events was 0.98 (95% CI 0.28 to 3.47; P = 0.97; I2 = 38%), indicating that cryotherapy is a safe intervention (Figure 6).</p> <p>Other outcomes see article.</p> <p>Author's Conclusion: The possible beneficial effect of cryotherapy on blood loss is too small to justify its use. There is evidence that cryotherapy improves knee range of motion and pain in the short-term. With a relatively small sample size of low quality evidence, it was dilicult to draw solid conclusions regarding the outcomes measured in this review, and specific recommendations cannot be made about the use of cryotherapy. This needs to be taken into account when considering the use of cryotherapy against its potential inconvenience and expense, particularly when more expensive automated forms of cryotherapy are used.</p>	<p>Albrecht 1997; Gibbons 2001; Kullenberg 2006; Levy 1993; Morsi 2002; Radkowski 2007; Smith 2002).</p>
Methodical Notes			

Funding Sources: • Sydney South West Area Health Service (Liverpool Hospital), Australia.  
Infrastructure, Salary  
• South West Sydney Clinical School, University of New South Wales, Australia.  
Infrastructure, Salary

COI: The authors declare they have no interests, financial or otherwise, that may impact on the findings of this review.

Study Quality: Study Quality was evaluated with the Cochrane risk of bias tool for each individual study and presented as GRADE summary of findings table for each end point. Quality was considered very low for all outcomes, except range of motion at discharge, which was considered low.

Heterogeneity: Heterogeneity was assessed using the chi-squared and I2 tests.  
Heterogeneity was investigated using subgroup analysis.

Publication Bias: Publication bias was investigated, but only in one outcome (blood loss), since the required amount of studies (n=10) to investigate was not available for the other outcomes.  
There was no evidence of publication bias.

Notes:

Oxford level of evidence level 1: systematic review and meta-analysis.  
No methodological caveats.

East, C. E. et al. Local cooling for relieving pain from perineal trauma sustained during childbirth. Cochrane Database of Systematic Reviews. . . 2012

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis.</p> <p>Databases: Cochrane Pregnancy and Childbirth Group's Trials Register, CENTRAL, MEDLINE; EMBASE; journals and the proceedings of major conferences;</p> <p>Search period: <u>1982-01.2012</u></p> <p>Inclusion Criteria: Published and unpublished randomised and quasi-randomised trials (RCTs) that compared localised cooling treatment applied to the perineum with no treatment or other treatments applied to relieve pain related to perineal trauma sustained during childbirth.</p> <p>Exclusion Criteria: -</p>	<p>Population: Women with perineal trauma (tear or episiotomy, or both) sustained during childbirth.</p> <p>Characteristics: 10 studies included No(involving 1825 women), which reported outcomes of cooling treatments (ice, cold gel pad or cold bath),</p> <p>Intervention: Application of localised cooling treatment to the perineum</p> <p>Comparison: versus no treatment, or other treatments to the perineum.</p>	<p>Primary: (1) Perineal pain, as measured by the trial authors, at the following time periods (or as close to the time period as possible):</p> <ul style="list-style-type: none"> <li>• within four to six hours of giving birth;</li> <li>• within 24 hours of giving birth;</li> <li>• between 24 and 72 hours of giving birth;</li> <li>• between three and 14 days aCer giving birth;</li> <li>• three months aCer giving birth.</li> </ul> <p>Secondary: (2) Perineal pain, as measured by the trial authors, associated with activities of daily living (for example, sitting, walking, urinating, caring for baby):</p> <ul style="list-style-type: none"> <li>(3) Painful sexual intercourse at three months postpartum.</li> <li>(4) Additional analgesia for relief of perineal pain:</li> <li>(5) Perineal oedema, as measured by the study authors periods (or as close to the time period as possible):</li> <li>(6) Perineal bruising, as measured by the study authors:</li> <li>(7) Adverse eHects on perineal healing, as measured by the study authors.</li> <li>(8) Side eHects severe enough to discontinue treatment.</li> <li>(9) Cost of treatment.</li> <li>(10) Women breastfeeding at:</li> <li>(11) Adverse eHects on mother-baby interactions, as measured by the study authors.</li> <li>(12) Maternal views and experiences with treatment, as measured by the study authors.</li> <li>(13) Maternal length of postnatal stay.</li> <li>(14) EHects on maternal quality of life, as measured by the study authors.</li> <li>(15) Women with postnatal depression.</li> <li>(16) Maternal exhaustion, as measured by the study authors</li> </ul> <p>Results: Note: only primary outcome in this section, see full article for the secondary outcomes.</p> <p>Primary: <u>Comparisons 1 and 2: Cooling treatment (ice pack or cold gel pad) versus no treatment</u></p> <p>3 trials compared the application of ice packs to the perineum (n = 145) with no treatment (n = 139). The only prespecified outcome with data suitable for inclusion in RevMan 2011 from the Leventhal 2011 report was the mean difference in pain score 60 minutes aCer the intervention that had occurred between two and 48 hours after giving birth. This favoured the ice pack group (mean difference (MD) -1.60; 95% confidence interval (CI) -2.57 to -0.63; one study, 76 women; Analysis 1.5) on a pain scale of zero (no pain) to 10 (worst pain). The group receiving ice packs in the study by Steen 2002 reported statistically significantly less self-reported moderate or severe pain between 24 and 72 hours aCer giving birth compared with women receiving no treatment (risk ratio (RR) 0.61; 95% CI 0.41 to 0.91; one study, 208 women;). This was not noted in the smaller study by Nawabi 2009 (n = 74). There were no statistically significant</p>	<p>Gallie 2003; Hill 1989; Leventhal 2011; Moore 1989; Nawabi 2009; Sheikhan 2011; Steen 2000; Steen 2002; Thangaraju 2006; Yasumran 2007;</p>

differences in perineal pain at other times.

**Comparison 3: Two cooling treatments (ice packs and cold gel pads)**  
 Three studies compared different forms of cooling therapy: ice packs (n = 164) and cold gel pads (n = 174). There were no statistically significant differences detected in perineal pain.

**Comparison 4: Cooling treatment (ice pack) versus pulsed electromagnetic energy.**  
 Gallie 2003 reported that women had statistically significantly more pain 24 to 72 hours following birth when treated with ice packs (n = 50) compared with pulsed electromagnetic energy (PET) (n = 50) (RR 5.60; 95% CI 2.35 to 13.33; one study, 100 women).

**Comparison 5: Cooling treatment (ice pack) versus hamamelis water (witch hazel)**  
 Moore 1989 reported no differences in women reporting none or mild pain relief from treatment with ice packs (n = 69) or hamamelis water (n = 77).

**Comparison 6: Cooling treatment (ice pack) versus pramoxine/hydrocortisone (Epifoam)**  
 2 studies compared ice packs (n = 91) and pramoxine/hydrocortisone topical aerosol foam (Epifoam) (n = 98). There were no differences in women's self-reported pain at any of the times measured.

**Comparison 8: Cooling treatment (cold gel pad) + compression versus gel pad + compression**  
 1 study (Yasumran 2007) considered both the cooling and compression components of treatments commonly applied to soft tissue injuries, for 250 women. This approach generally also includes rest and elevation. In the intervention group, cold gel pads were placed in a cotton sleeve and held in place with a special belt to facilitate compression. In the control group the gel pads were not cooled prior to being applied with compression. The cold gel pad and compression had more favourable outcomes than the gel pad and compression in terms of women's self-reported pain between 24 and 72 hours of giving birth (MD -0.43; 95% CI -0.73 to -0.13; Analysis 8.2).

**Comparison 9: Cooling treatment (cold gel pad, ice pack or cold bath) versus warmth (warm pack or warm bath)**  
 Women reported a mean reduction of -1.36 (95% CI -2.17 to -1.55; Analysis 9.1) for perineal pain within 24 hours of giving birth following the use of cold gel pads, compared with a warm bath plus Betadine and between three and 14 days after giving birth (MD -2.40, 95% CI -3.26 to -1.54, Analysis 9.2) in one small study (Sheikhan 2011, n = 60). This outcome was not reported in the study by Hill 1989, that compared the use of a ice or cold bath with a warm pack or warm bath.

**Author's Conclusion:** There is limited evidence to support the use of cooling treatments, in the form of ice packs or cold gel pads, for the relief of perineal pain following childbirth. It is likely that concurrent use of several treatments is required to adequately address this issue, including topical lignocaine, prescription and non-prescription analgesia, ultrasound or pulsed electromagnetic energy (East 2011; Sleep 1988). Current evidence to support the efficacy of some of these treatments is also limited. However, their use, as for ice packs, remains relatively common (East 2011; Sleep 1988). Studies included in this review involved the use of cooling treatments for 10 to 20 minutes, and although no adverse effects were noted, these findings came from studies of relatively small numbers of women.

## Methodical Notes

**Funding Sources:** Internal sources  
 • Queensland Health Nursing Research Grant, Australia.  
 External sources  
 • No sources of support supplied

**COI:** Paul Marchant collaborated in randomised controlled trials comparing the effectiveness of two cooling treatments for the relief of perineal pain following childbirth. These reports were included in the review (Steen 2000; Steen 2002) but were reviewed by other authors.

**Study Quality:** Assessment of study quality by two investigators using Cochrane risk of bias tool.  
 "The overall quality of the reported studies was poor, with improvement in some of the later studies. The main area of concern was the lack of detail provided on randomisation sequence generation and the nature of the interventions that necessitated non-blinding of the participants and their clinicians. Attempts were made by some investigators to blind outcome assessors."

**Heterogeneity:** "We assessed statistical heterogeneity in each meta-analysis using the TU, IU and ChiU statistics. We regarded heterogeneity as substantial if IU was greater than 30% and either TU was greater than zero, or there was a low P value (less than 0.10) in the ChiU test for heterogeneity."  
 We explored heterogeneity using sensitivity analysis. A random-effects metaanalysis was used as an overall summary if considered appropriate.

**Publication Bias:** Investigations of publication bias using Funnel plots and Egger test, but were omitted since the number of articles per outcome was insufficient (lower than 10.)

**Notes:**

Oxford level of evidence 1: sytematic review and meta-analysis.

Notes: No overall or individual population characteristics are provided.(age, previous births, mode of birth, ethnicity, BMI, etc).

Although some are investigated in subgroup analysis.

**Schlüsselfrage:**

**3.3.1.4 TENS**

Fragestellung wird durch LL-Adaptation aktualisiert. Zusätzlich wurde in 2020 eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

**Inhalt: 2 Literaturstellen**

Literaturstelle	Evidenzlevel	Studientyp
Johnson, M. I. 2015	1	Systematic review and meta-analysis of RCTs (0 studies included).
Johnson, M. I. 2015	1	SR and META (of 19 trials, 12 from earlier version and seven new trials in this update)

**OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)**

Johnson, M. I. et al. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. Cochrane Database of Systematic Reviews. . . 2015			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level: 1</b></p> <p><b>Study type:</b> Systematic review and meta-analysis of RCTs (0 studies included).</p> <p><b>Databases:</b> Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, AMED, CINAHL, PEDRO and SPORTDiscus</p> <p><b>Search period:</b> 2010 (last version) - 2015.</p> <p><b>Inclusion Criteria:</b> We only included RCTs investigating the use of TENS for the management of phantom pain and stump pain following an amputation in adults.</p> <p><b>Exclusion Criteria:</b> -</p>	<p><b>Population:</b> -</p> <p><b>Intervention:</b> transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain.</p> <p><b>Comparison:</b></p> <ul style="list-style-type: none"> <li>• no treatment controls.</li> <li>• sham controls (defined as any electrotherapeutic device that has been modified so that there is no active output (i.e. dummy device).</li> <li>• pharmacological intervention.</li> <li>• non-pharmacological intervention.</li> </ul>	<p><b>Primary:</b> Patient-reported pain using standard subjective validated scales (e.g. visual analogue scales (VAS) or numerical rating scales (NRS)).</p> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• Any other related pain measure designed to capture data pertaining to the characteristics and quality of pain (e.g. McGill Pain Questionnaire)</li> <li>• Patient reported non-painful phantom sensations using validated scales</li> <li>• Patient satisfaction</li> <li>• Activities of daily living and ambulation</li> <li>• Range of movement*</li> <li>• Quality of life</li> <li>• Anxiety/depression</li> <li>• Use of pain coping strategies</li> <li>• Sleep**</li> <li>• Analgesic consumption</li> <li>• Hospital attendance</li> <li>• Other healthcare interventions, e.g. physiotherapy visits, hospice admissions, day care etc</li> <li>• Any adverse effects</li> </ul> <p><b>Results:</b> -</p> <p><b>Author's Conclusion:</b> Implications for practice Since publication of the original version of this review, we have found no new trials. There is insufficient evidence from RCTs to judge whether TENS should, or should not, be used in the management of phantom pain and stump pain in adults.</p>	-
<b>Methodical Notes</b>			
<p><b>Funding Sources:</b> Cochrane Review Group funding acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. <b>Disclaimer:</b> The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health.</p> <p><b>COI:</b> Mark I Johnson has no conflicts of interest to declare. Matthew R Mulvey has no conflicts of interest to declare. Anne-Marie Bagnall has no conflicts of interest to declare.</p>			



Study Quality: There were no trials included in this review so risk of bias could not be evaluated.

Heterogeneity: -

Publication Bias: -

Notes:

Oxford level of evidence: 1

Notes: The article represents an update to the existing Cochrane systematic review from 2010. Notably, it does not include any studies from that period, or any from before 2010. Therefore it is basically a study protocol and can only be of limited use in decision making.

Recommend exclusion.

Johnson, M. I. et al. Transcutaneous electrical nerve stimulation for acute pain. Cochrane Database of Systematic Reviews. . . 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: SR and META (of 19 trials, 12 from earlier version and seven new trials in this update)</p> <p>Databases: he Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; MEDLINE; EMBASE; CINAHL; and AMED. We also checked the reference lists of included trials.</p> <p>Search period: up to 3 December 2014</p> <p>Inclusion Criteria: Randomised controlled trials (RCTs), TENS given as a sole treatment and assessed pain with subjective pain scales.</p> <p>Exclusion Criteria: - trials on experimental pain, case reports, clinical observations, letters, abstracts or reviews. - trials investigating the effect of TENS on pain during childbirth (labour), primary dysmenorrhoea or dental procedures. - Studies where TENS was given with another treatment as part of the formal trial design</p>	<p>Population: Adults with acute pain (&lt; 12 weeks) if they examined TENS given as a sole treatment and assessed pain with subjective pain scales.</p> <p>The effect of TENS was investigated on procedural pain, including:</p> <ul style="list-style-type: none"> <li>- cervical laser treatment</li> <li>- office hysteroscopy</li> <li>- screening flexible sigmoidoscopy</li> <li>- flexible cystoscopy</li> <li>- nsedated colonoscopy</li> <li>- venepuncture</li> </ul> <p>The remaining trials investigated the effect of TENS on</p> <ul style="list-style-type: none"> <li>- haemophilia pain</li> <li>- acute trauma such as sprains or fractures,</li> <li>- postpartum uterine contractions,</li> <li>- acute low back pain (LBP) during pregnancy</li> <li>- acute orofacial pain,</li> <li>- post thoracotomy,</li> <li>- post-cardiac surgery</li> <li>- post-episiotomy</li> <li>- rib fractures</li> <li>- neuropathic pain.</li> </ul> <p>Intervention: - TENS versus</p>	<p>Primary: Standard subjective scales for pain intensity, pain relief or both (e.g. visual analogue scales (VAS), numerical rating scales (NRS); verbal rating scales (VRS) McGill Pain Questionnaire (MPQ)).</p> <p>Secondary: Other measures of pain.</p> <p>Results: TENS vs Placebo outcome Pain intensity (100mm VAS): 6 trials included; MD -24.62 95% CI (-31.79,-17.46) favours TENS. Heterogeneity Tau<sup>2</sup> = 58.21; Chi<sup>2</sup> = 18.13, df = 6 (P = 0.006); I<sup>2</sup> = 67%. Test for overall effect: Z = 6.73 (P &lt; 0.00001) (Outcome measurement and TENS treatment varied between groups).</p> <p>TENS vs Placebo, outcome &gt;50% reduction in pain: 4 trials included; RR 3.91 95% CI (2.42, 6.32) favours TENS. Heterogeneity: Chi<sup>2</sup> = 0.84, df = 6 (P = 0.99); I<sup>2</sup> = 0%. Test for overall effect: Z = 5.58 (P &lt; 0.00001)(Outcome measurement and TENS treatment varied between groups).</p> <p>TENS vs no treatment control, outcome pain intensity (100mm VAS): 5 trials included; MD -19.05 95% CI (-27.30, -10.79) Favours TENS; Heterogeneity: Tau<sup>2</sup> = 85.32; Chi<sup>2</sup> = 20.87, df = 6 (P = 0.002); I<sup>2</sup> = 71%; Test for overall effect: Z = 4.52 (P &lt; 0.00001); Outcome measurement and TENS treatment varied between groups).</p> <p>All results showed high heterogeneity; other outcome data could not be pooled due to high heterogeneity.</p> <p>Author's Conclusion: This Cochrane Review update includes seven new trials, in addition to the 12 trials reviewed in the first update in 2011. The analysis provides tentative evidence that TENS reduces pain intensity over and above that seen with placebo (no current) TENS when administered as a stand-alone treatment for acute pain in adults. The high risk of bias associated with inadequate sample sizes in treatment arms and unsuccessful blinding of treatment interventions makes definitive conclusions impossible. There was incomplete reporting of treatment in many reports making replication of trials impossible.</p>	<p>Seven new trials:</p> <ul style="list-style-type: none"> <li>- Amer-Cuenca 2011;</li> <li>- de Sousa 2014;</li> <li>- Ekblom 1987;</li> <li>- Gregorini 2010;</li> <li>- Keskin 2012;</li> <li>- Kim 2012;</li> <li>- Pitanguí 2012.</li> </ul> <p>Trials already included in previous versions of this review:</p> <ul style="list-style-type: none"> <li>- Cheing 2005;</li> <li>- Coyne 1995;</li> <li>- Crompton 1992;</li> <li>- De Angelis 2003;</li> <li>- Hansson 1983;</li> <li>- Hruby 2006;</li> <li>- Limoges 2004;</li> <li>- Liu 1985;</li> <li>- Olsén 2007;</li> <li>- Oncel 2002;</li> <li>- Ordog 1987;</li> <li>- Roche 1985.</li> </ul>

placebo TENS - TENS versus no treatment controls - TENS versus a pharmacological intervention - TENS versus a non- pharmacological intervention.  Comparison: see intervention.	
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## Methodical Notes

**Funding Sources:** See text.

**COI:** Three authors had nothing to declare, one acts as a consultant for DJO, Inc. (declaration approved by the Cochrane Funding Arbiter).

**Study Quality:** Methodological quality was assessed with Cochrane Collaboration's 'Risk of bias' assessment tool as described in Chapter 8 of Higgins 2011.

In cases of missing data due to withdrawals or dropouts, we only used the data analysed in the trial for analysis in this Cochrane Review.

Overall there was a high risk of bias due to sample size (small groups) and in Blinding of participants.

**Heterogeneity:** We planned to test heterogeneity between comparable trials using a standard Chi<sup>2</sup> test considered statistically significant at a P value < 0.1.

We interpreted the I<sup>2</sup> statistic value according to the following thresholds (Higgins 2011):

- 0% to 40%, might not be important;
- 30% to 60%, may represent moderate heterogeneity;
- 50% to 90%, may represent substantial heterogeneity; and
- 75% to 100%, considerable heterogeneity.

**Publication Bias:** Not assessed.

### Notes:

CEBM Oxford Level of Evidence (2011): EL 1 (SR of RCT's).

### Limitations:

- small study groups
- unsuccessful blinding
- high heterogeneity

Due to the limitations the results should be interpreted with caution.

Schlüsselfrage:

3.3.1.5 Akupunktur

Fragestellung wird durch LL-Adaptation aktualisiert. Zusätzlich wurde in 2020 eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

Inhalt: 6 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Brown, J. 2014	1	Systematic review including only other Cochrane systematic reviews (17 in total).
Eccleston, C. 2017	1	Systematic review without meta-analysis (5 studies)
Green, S. 2005	1	Systematic review and meta-analysis.
Griffiths, J. D. 2012	1	Systematic review and meta-analysis (52 studies, 41 in the meta-analysis)
Kwan, I. 2018	1	Systematic review and meta-analysis
Lee, A. 2015	1	Systematic review and meta-analysis (59 articles)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 6 Bewertung(en)

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Brown, J. et al. Endometriosis: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. . . 2014</b></p> <p><b>Evidence level: 1</b></p> <p><b>Study type: Systematic review including only other Cochrane systematic reviews (17 in total). Databases: Cochrane library</b></p> <p><b>Search period: 03/2014</b></p> <p><b>Inclusion Criteria: Only Cochrane reviews were considered for inclusion in this overview. Cochrane protocols and titles were identified for future inclusion.</b></p> <p><b>Exclusion Criteria: -</b></p>	<p><b>Population:</b> Eligible participants were premenopausal women with a clinical diagnosis of endometriosis who had sought medical attention for pain or subfertility, or both. Women with endometriomata who had sought medical attention for pain or subfertility, or both, were also included.</p> <p><b>Intervention:</b> <u>Interventions for pain relief</u> Medical treatments, complementary therapies or surgical interventions (including excisional and ablative surgery for endometriomata) were considered. Medical and complementary therapies could be used as single interventions or administered pre or post-operatively, or both. <u>Interventions for subfertility</u> Medical treatments, complementary therapies or surgical interventions (including excisional and ablative surgery for endometriomata) were considered. Medical and complementary therapies could be used as a single</p>	<p><b>Primary: <u>Outcomes for pain relief:</u></b> self reported pain relief for dysmenorrhoea <b><u>Outcomes for subfertility:</u></b> live birth, clinical pregnancy, ongoing pregnancy, miscarriage, adverse events.</p> <p><b>Secondary: <u>Outcomes for pain relief:</u></b> clinical improvement or resolution of endometriosis-related pain; pain recurrence, adverse events.</p> <p><b>Results: Primary:</b> Pain outcomes (other outcomes see article). <b><u>1.1 Gonadotrophin-releasing hormone agonist or antagonist (GnRHa)</u></b> Brown 2010 concluded that women receiving GnRHAs were more likely to achieve symptom relief than those having no treatment risk ratio (RR) 3.93, 95% confidence interval (CI) 1.37 to 11.28). There was no statistically significant difference between GnRHAs <b><u>1.2 Ovulation suppression</u></b> see article <b><u>1.3 Analgesics Non-steroidal anti-inflammatory drugs (NSAIDs)</u></b> Allen 2009 reported inconclusive evidence on the effectiveness of NSAIDs (naproxen) when compared with placebo based on the management of pain associated with endometriosis (OR inverse variance 0.33, 95% CI 0.61 to 17.69, 20 participants, 1 trial). <b><u>1.4 Surgical interventions</u></b> Laparoscopic surgery was associated with decreased overall pain (measured as 'pain better or improved') compared with diagnostic laparoscopy, both at 6 months (OR 6.58, 95% CI 3.31 to 13.10) and at 12 months (OR 10.00, 95% CI 3.21 to 31.17). When laparoscopic ablation was compared with diagnostic laparoscopy plus medical therapy (GnRHa with add back therapy), more women in the ablation group were pain free at 12 months</p>	<p>17 systematic reviews included, see article.</p>

intervention or administered pre or post-operatively, or both.

Comparison: interventions compared against another.

(OR 5.63, 95% CI 1.18 to 26.85). The difference between laparoscopic ablation and laparoscopic excision in the proportion of women reporting overall pain relief at 12 months on a VAS 0 to

10 pain scale was 0 (95% CI to 1.22 to 1.22).

#### 1.5 Post-surgical interventions

Lu 2012 found no evidence of a benefit from pentoxifylline when compared with no treatment on the reduction of pain associated with endometriosis aDer laparoscopic surgery in one randomised trial; and neither was there evidence of a diKerence between pentoxifylline and placebo aDer surgery on recurrence of disease, as reported in the single randomised trial. The mean reduction

in pain at three months was 5.53 in the control group. In the intervention group the mean pain reduction was 1.6 lower (range 3.32 lower to 0.12 higher, 34 participants, 1 trial).

Furness 2004 found no evidence of a benefit from pre-surgical medical therapy compared to surgery alone for the symptomatic

relief of endometriosis, or for post-surgical hormone suppression compared with surgery alone for the pain and disease recurrence outcomes. There was also no evidence that pre-surgical hormone suppression was diKerent to post-surgical hormone suppression for the outcome of pain, and there were no diKerences in AFS scores in a comparison of post-surgical medical therapy and pre and postsurgery therapy.

#### 1.6 Other medical intervention

Anti-tumour necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) Lu 2013 found no evidence to support the use of anti-TNF-L drugs for the alleviation of pain associated with endometriosis. The evidence was based on a single trial. The patient Biberoglu and Behrman score was a mean of 1.7 in the control group and 0.2 lower

in the intervention group (range 0.68 lower to 0.28 higher).

#### 1.7 Other interventions

Zhu 2011 reported on one trial of 67 women. The trial found that auricular acupuncture was significantly more eKective at reducing pain associated with endometriosis than Chinese herbal medicine (RR 3.04, 95% CI 1.65 to 5.62, 67 participants, 1 trial).

Flower 2012 reported on two post-surgical interventions using Chinese herbal medicine. The authors concluded that Chinese herbal medicine may have comparable benefits to conventional medicine (gestrinone and danazol) but with fewer side eKects. Chinese herbal medicine appeared to have some superiority over danazol in the relief of symptoms. The review was based on only two randomised trials.

#### **Author's Conclusion: Implications for practice**

For women with pain and endometriosis, suppression of menstrual cycles with GnRH analogues, LNG-IUD and danazol was beneficial. Laparoscopic treatment of endometriosis and excision of endometriomata were associated with pain improvements and therefore surgical approaches can be considered. There are no medical treatments that are recommended to improve natural fertility in women with endometriosis. Women who are undergoing ART and who have known endometriosis could be treated with three months of a GnRH agonist, as this may improve

pregnancy outcomes. Laparoscopic surgery improved fertility outcomes compared to diagnostic laparoscopy. There is insufficient evidence about the surgical treatment of endometriosis in women undergoing ART interventions.

#### **Methodical Notes**

##### **Funding Sources: Internal sources**

- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.

##### **External sources**

- Auckland District Health Board Charitable Trust, New Zealand.

COI: None

**Study Quality:** The quality of the included reviews was assessed using the AMSTAR tool (Shea 2007). We also noted in each case whether the literature search had been conducted or updated within the past three years (to March 2014).

The quality of the evidence reported by the primary studies in the included reviews was rated using GRADE methods and ranged from very low to moderate for individual comparisons.

Heterogeneity: -

Publication Bias: -

Notes:

Oxford level of evidence 1: systematic review and meta-analysis.

This article in itself does not represent a systematic review, instead it requires the articles included (also Cochrane SR) to be comprehensive and systematic, which introduces an unnecessary bias in my opinion.

It is unclear why this approach was chosen. The quality of the included studies was graded at least.

Eccleston, C. et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. Cochrane Database of Systematic Reviews. . . 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review without meta-analysis (5 studies)</p> <p>Databases: CENTRAL, MEDLINE, Embase, grey literature.</p> <p>Search period: last version (2013) - 01/2017</p> <p>Inclusion Criteria: Included studies had to be randomised controlled trials comparing opioid users receiving an intervention with a control group receiving treatment as usual, active control, or placebo. The aim of the study had to include a treatment goal of dose reduction or cessation of opioid medication.</p> <p>Exclusion Criteria: studies involving only participants with issues of addiction, abuse, dependence, or non-prescribed opioid use, and involving participants using opioids for pain relief during palliative care. This is because the aims of treatment for these populations differ substantially from those for the population of interest.</p>	<p>Population: Participants were adults (18 years of age or older) using prescription opioids for management of CNCP with a duration of at least three months. Pain conditions could include but were not limited to: neuropathic pain, myofascial pain, back pain, fibromyalgia, headache, abdominal, neck or musculoskeletal pain.</p> <p>Intervention: Interventions could be based in pharmacology, physiology, psychology, spirituality, or another approach, provided that the underpinning methodology was well documented. Opioid antagonist treatment, dose tapering, or opioid replacement with other pain-relieving medication. Interventions could also involve physical therapy, massage, disability management, complementary therapies, or psychological approaches such as cognitive behavioural therapy, counselling, and coping techniques.</p> <p>Comparison: Any one of the interventions.</p>	<p>Primary: Primary outcomes</p> <ul style="list-style-type: none"><li>• prescribed opioid use in adults;</li><li>• adverse events related to opioid reduction</li></ul> <p>Secondary: Secondary outcomes</p> <ul style="list-style-type: none"><li>• pain intensity/severity;</li><li>• psychological functioning;</li><li>• physical functioning.</li></ul> <p>Results: Only results relevant to the guideline reported here. Other outcomes see article.</p> <p>Primary: <b>Adverse events</b></p> <p>Garland 2014 did not report the occurrence of adverse events. When we contacted the study authors, they reported that there had been no adverse events.</p> <p>Jamison 2010 reported adverse events across all participants of dry mouth (44.9%), constipation (38.4%) sweating (37.5%), memory lapse (28.4%), weakness (24.1%), itching (23.9%), and headaches (28.4%). The treatment group reported lower rates of constipation and itching, but higher vision problems. The control group reported more severe constipation, sneezing, and nightmares than the treatment group.</p> <p>Naylor 2010 did not report on adverse events, but contact with the study authors confirmed that there were no adverse events associated with treatment.</p> <p>Sullivan 2017 reported one severe study-related adverse event in the taper-support group. The study psychiatrist prescribed nortriptyline during the participant's initial psychiatric evaluation, which the participant had a severe reaction to. This medication was discontinued and symptoms resolved.</p> <p>Zheng 2008 reported a total of 33 adverse events during the treatment period with REA, and 19 with SEA, none of which were classed as serious adverse events. Opioid-based adverse events decreased from baseline to eight weeks after treatment by 40% in the REA group and 45% in the SEA group.</p> <p>Secondary: <b>Pain intensity</b></p> <p>Garland 2014 used the Brief Pain Inventory, pain intensity subscale and found that the MORE group reported significantly lower pain intensity at post-treatment (Mean (M) = 4.86, SD = 1.38) that met the threshold for minimally clinically significant change, in comparison to the support group (SG) control group (M = 5.71, SD = 1.58). This between-group difference was maintained at follow-up (MORE M = 4.77, SD = 1.95; SG M = 6.10, SD = 1.48).</p> <p>Jamison 2010 assessed pain using the Brief Pain Inventory, pain intensity subscale. However, post-treatment means and standard</p>	<p>Gaarland 2014; Jamison 2010; Naylor 2010; Sullivan 2017; Zheng 2008;</p>

deviations were not reported. reported in Naylor 2008 (Naylor 2010). The TIVR group reported a decrease in typical pain from baseline to eight months from 5.7/10 to 3.4/10, and the standard care control from 6.8 to 5.7. The difference between groups was statistically significant. Sullivan 2017 assessed pain intensity using the Brief Pain Inventory, pain severity subscale. There was no significant difference between groups at 22 weeks (taper support = 4.72 , SD = 1.62; usual care = 5.77, SD = 1.92) or at 34 weeks (taper support = 4.67 , SD = 1.79; usual care = 6.16, SD = 2.64). Zheng 2008 used the Visual Analogue Scale to assess pain intensity. Average pain at baseline was 4.9/10 in the experimental group and 5.6/10 in the control group, and post-treatment scores were 4.2 and 5.4, respectively. No differences were detected between groups. At 20 weeks average pain scores were 3.6 and 4.6.

**Author's Conclusion: Implications for practice**  
 There were too few data in this review to permit any comments about implications for practice.  
**Implications for research**  
**General implications**  
 There is an urgent need for more research. There is a growing population of people with chronic pain, who also have chronic use of opioids, which are thought to be untherapeutic and for whom reduction is a primary clinical goal. We are unable to reduce our uncertainty around any treatment offered to these people for this purpose.

**Methodical Notes**

**Funding Sources:** Internal sources  
 • Oxford Pain Relief Trust, UK.  
 Institutional support  
 External sources  
 • No sources of support supplied

**COI:** several, see article.

**Study Quality:** Quality investigation was planned, but not performed, because the meta-analysis was dropped. "The evidence base identified by this review is small and limited and we were unable to perform a GRADE assessment of the certainty of evidence in this area. The individual studies have small numbers of participants, and overall we have evidence of the experience of only 278 chronic pain patients. There is a heterogeneity of interventions and outcome reporting. Poor reporting is common, meaning that the risk of bias was often unclear or high."

**Heterogeneity:** no meta-analysis was performed.

**Publication Bias:** "We planned to assess publication bias by estimating the number of unpublished null studies needed to make a clinical finding likely to be unstable or irrelevant (Moore 2008). Unfortunately, this was not possible because we were not able to calculate any effect sizes."

**Notes:**  
 Oxford level of evidence: 1 Systematic review and meta-analysis.  
 No meta-analysis was performed, due to little available data.

**Green, S. et al. Acupuncture for shoulder pain. Cochrane Database of Systematic Reviews. . . 2005**

Evidence Types	level/Study	P - I - C	Outcomes/Results	Literature References
Evidence level: 1  Study type: Systematic review and meta-analysis. Databases: MEDLINE, EMBASE, CINAHL,		Population: a) Adults >16 years of age. b) Shoulder pain or disorder for greater than 3 weeks, irrespective of diagnostic label (unless an exclusion	Primary: No studies were excluded on the basis of outcome measure used. Outcomes reported in trials were pain, time to maximum pain relief, shoulder discomfort, range of motion (external and internal rotation, flexion, extension, and abduction), shoulder function,	18 studies, see article.

(SCISEARCH) were searched.

Search period: inception to December 2003.

Inclusion Criteria: Study types:

a) Randomised or quasi-randomised controlled trials regardless of publication type.

b) Trials in which allocation to intervention or control group was not concealed from the outcome assessor were included but recorded as such in the table of included studies.

c) Studies in all languages were translated into English and considered for inclusion in the review.

Types of participants

a) Adults >16 years of age.

b) Shoulder pain or disorder for greater than 3 weeks, irrespective of diagnostic label (unless an exclusion criteria). Studies that included various soE tissue disorders were considered if the results on shoulder pain were presented separately or if 90% or more of participants in the study had shoulder pain.

c) Studies of participants suffering a history of significant trauma or systemic inflammatory conditions such as rheumatoid arthritis, polymyalgia rheumatica and fracture, hemiplegic shoulders, postoperative and peri-operative shoulder pain and pain in the shoulder.

Types of interventions

All randomised controlled comparisons of acupuncture versus placebo, no treatment, another intervention, or of varying types and dosages of acupuncture compared to each other were included and comparisons established according to intervention

Types of outcome measures

No studies were excluded on the basis of outcome measure used. Outcomes reported in trials were pain, time to maximum pain relief, shoulder discomfort, range of motion (external and internal rotation, flexion, extension, and abduction), shoulder function, success or failure of treatment, and adverse events.

Exclusion Criteria: Studies where participants were not randomised into intervention groups were excluded from the review.

criteria). Studies that included various soE tissue disorders were considered if the results on shoulder pain were presented separately or if 90% or more of participants in the study had shoulder pain.

c) Studies of participants suffering a history of significant trauma or systemic inflammatory conditions such as rheumatoid arthritis, polymyalgia rheumatica and fracture, hemiplegic shoulders, postoperative and peri-operative shoulder pain and pain in the shoulder.

Intervention: All randomised controlled comparisons of acupuncture versus placebo, no treatment, another intervention, or of varying types and dosages of acupuncture compared to each other were included and comparisons established according to intervention

Comparison: Placebo, no treatment, other intervention than acupuncture.

success or failure of treatment, and adverse events.

Secondary: not described

Results: ACUPUNCTURE COMPARED TO PLACEBO

2 trials assessed success rate of acupuncture in the short term for rotator cuff disease. There was no significant difference between success rates in the acupuncture group compared to the placebo group (RR 1.01 (0.69 to 1.48)). Nor was there a significant difference between acupuncture and placebo in reducing pain or increasing the range of abduction in the short term. One small trial did demonstrate a significant difference post intervention (4 weeks) favouring the acupuncture group for improved shoulder pain, range of movement and functioning

measured by a composite score of these factors (WMD 17.3 (7.79, 26.81)). At four months follow-up a significant difference remained between the groups, however the difference between the change in scores in the acupuncture group and the change in scores in the placebo group was unlikely to be clinically significant (WMD 3.53(0.74 to 6.32)) (i.e.. a change of 3.53 on a scale of 100 is unlikely to represent a clinically significant improvement).

ACUPUNCTURE COMPARED TO STEROID INJECTION

One trial compared acupuncture to anterior glenohumeral injection of corticosteroid for rotator cuC disease, with only 12 participants in each group (Berry 1980). There was no significant difference from placebo following treatment with respect to pain (WMD 7.5 (-12.47 to 27.47)), range of abduction (WMD 2.9 (-26.83 to 32.62) or success rate (RR 0.83 (0.35 to 2.00)).

ACUPUNCTURE COMPARED TO ULTRASOUND

The same trial (Berry 1980) with 12 participants per group compared acupuncture to ultrasound and demonstrated no significant difference between groups following treatment with respect to pain (WMD -7.10 (-32.90 to 18.70)), range of abduction

(WMD 7.9 (-21.59 to 37.39) or success rate (RR 0.83 (0.35 to 2.00)).

ELECTROACUPUNCTURE COMPARED TO STELLATE GANGLION BLOCK AND SUPRASCAPULAR NERVE BLOCK

A trial of 100 participants with adhesive capsulitis, published in Chinese, investigated the relative effects of electroacupuncture and regional nerve block (anaesthesia of stellate ganglion and suprascapular nerve). There was a significant difference favouring nerve block over acupuncture in reducing pain at 3 hours follow-up (WMD 1.33 (1.22 to 1.44 )) (out of 4).

The time to achieve maximum pain relief was significantly shorter in the nerve block group (WMD 64.96 (60.50 to 69.42 minutes)). There was a statistically significant but small difference favouring nerve block in increasing range of flexion (WMD -7.00 (-11.17 to -2.83)).

No adverse effect was assessed for either intervention. This trial gives no information as to the relative effect of either intervention compared to no treatment or placebo.

ACUPUNCTURE PLUS MOBILISATION VERSUS ACUPUNCTURE ALONE

In a pilot study of participants with general shoulder pain (of no particular diagnosis) (Romoli 2000), eight in the acupuncture plus mobilization group and eight in the mobilization only group, results post intervention revealed no significant difference between the acupuncture plus mobilization

compared to mobilization alone with respect to pain at rest (WMD -0.37(-1.85 to 1.11)), pain on movement (WMD 0.25 (-1.87 to 2.37)) (out of a total of 10), or active flexion (WMD -13.13(-39.79 to 13.53) and abduction (WMD -14.37 (-49.94 to 21.20)). No longer term follow-up data were provided by the trialist, nor is there information regarding the effect of either intervention compared to placebo or no treatment.

#### ACUPUNCTURE PLUS EXERCISE VERSUS EXERCISE ALONE

A small trial comparing acupuncture and exercise with exercise alone for adhesive capsulitis (Sun 2001) showed a significant difference favouring the acupuncture plus exercise group in a composite measure of pain, range of motion and functioning post intervention (WMD 9.20 (0.54 to 17.86)) (out of a total score of 100). The effect remained at 20 weeks follow-up (WMD 9.40 (0.52 to 18.28)).

#### ACUPUNCTURE VERSUS TRAGAR

One trial compared acupuncture and Tragar for the treatment of general shoulder pain (no particular diagnosis) due to wheel chair use (Dyson-Hudson 2001). There were no significant differences in pain scores post intervention (WMD 1.70 (-21.91 to 25.31)) or at five weeks follow-up (WMD 16.00 (-9.03 to 41.03)) (out of a total of 150) between the groups. This trial provides no information about

the benefits of acupuncture or Tragar compared to placebo or no intervention.

#### DEEP VERSUS SHALLOW ACUPUNCTURE

In a trial comparing deep acupuncture and shallow acupuncture in those with general shoulder pain (no particular diagnosis) there was a significant difference favouring deep acupuncture over shallow acupuncture with respect to pain post intervention (WMD -10.31 (-15.44 to -5.18)) and at three months follow-up (-8.00 (-12.20 to -3.80)). Pain was recorded using the Mc Gill Pain Questionnaire (Melzack 1975) (Ceccherelli 2001).

#### JING LUO VERSUS TRADITIONAL CHINESE MEDICINE ACUPUNCTURE

There was a significantly greater recovery rate in the group where acupuncture sites were determined according to the distribution of Jing Luo compared to sites determined according to pathogenesis in the theory of traditional Chinese medicine (RR 1.50 (1.08 to 2.09)) for peri-arthritis (Yuan 1995). This trial gives no information about the benefits of acupuncture compared to placebo or no treatment.

**Author's Conclusion: Implications for practice**  
Due to a small number of clinical and methodologically diverse trials, little can be concluded from this review. There is little evidence to either support or refute the use of acupuncture for treating shoulder pain and more trials are needed. The limited evidence available indicates some short term benefit of acupuncture compared to placebo with respect to shoulder specific disability. Little is known of the potential for adverse effects.

#### Methodical Notes

Funding Sources: Internal sources  
• Australasian Cochrane Centre, Monash University, Australia.

COI: No author involved in this review has any known conflict of interest in regard to this review.

Study Quality: Trial quality was not scored numerically.



The only quantitative scoring was given for allocation concealment, ranked as: A: adequate B: unclear, or C: inadequate.

Trial quality was assessed in this qualitative way as opposed to using a numerical or summary scale due to concerns regarding the validity of such scales and lack of information about whether all the criteria included in such scales impact on the overall outcome of the trial.

"Included studies were of varying methodological quality."

Heterogeneity: possible clinical and methodological reasons for heterogeneity were explored, and in the presence of significant heterogeneity, trial results were not combined.

Publication Bias: not investigated.

Notes:

Oxford level of Evidence: 1 Systematic review and meta-analysis.

Note: relatively old review (searches up to 2003); no investigation of publication bias.

Griffiths, J. D. et al. Interventions for preventing nausea and vomiting in women undergoing regional anaesthesia for caesarean section. Cochrane Database of Systematic Reviews. . . 2012

Evidence Types	level/Study	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (52 studies, 41 in the meta-analysis)</p> <p>Databases: Cochrane Pregnancy and Childbirth Group's Trials Register, which includes data from CENTRAL, MEDLINE, EMBASE, journals on the topic.</p> <p>Search period: Inception - 02/2012</p> <p>Inclusion Criteria: We included published and unpublished randomised controlled trials (RCTs), including cluster-randomised trials. Pregnant women undergoing elective or emergency caesarean section under regional anaesthesia. We included studies where the intervention was given with the express purpose of preventing either intraoperative or postoperative nausea and vomiting, or both. We compared the various interventions with placebo or no treatment, and with each other.</p> <p>Exclusion Criteria: Quasi-RCTs and cross-over studies were excluded. We excluded studies where the express purpose was to treat another problem which may impact upon the development of nausea or vomiting, such as studies assessing agents for treating hypotension. Studies which assess the efficacy of these interventions for treatment (rather than prevention) of nausea and vomiting will be</p>	<p>Population: Pregnant women undergoing elective or emergency caesarean section under regional anaesthesia.</p> <p>Intervention: 1. Serotonin (5-HT3) receptor antagonists (e.g. ondansetron, granisetron). 2. Dopamine receptor antagonists (e.g. metoclopramide, prochlorperazine, droperidol, domperidone). 3. Corticosteroids (e.g. dexamethasone). 4. Antihistamines (e.g. promethazine, cyclizine). 5. Anticholinergic agents (e.g. glycopyrrolate, scopolamine). 6. Sedatives (e.g. midazolam, propofol). 7. Opioids (e.g. nalbuphine) 8. Supplemental oxygen. 9. Intravenous fluids. 10. Acupuncture/acupressure.</p> <p>Comparison: each intervention compared with against each other</p>	<p>Primary: 1. Nausea intraoperatively. 2. Vomiting (and/or retching) intraoperatively. 3. Nausea postoperatively. 4. Vomiting (and/or retching) postoperatively</p> <p>Secondary: 1. Maternal adverse effects: e.g. sedation, restlessness, extrapyramidal effects, surgical bleeding, hypotension, atonic uterus. 2. Neonatal morbidity: e.g. Apgar scores less than seven at five minutes. 3. Initiation of breastfeeding. 4. Duration of exclusive breastfeeding. 5. Maternal satisfaction (using a validated questionnaire).</p> <p>Results: Due to length only the summaries are presented here, for the others see the article. A. 5-HT3 antagonists. Using data from 10 studies involving 980 women, overall we found that 5-HT3 antagonists were effective in reducing intraoperative nausea, and postoperative nausea and vomiting. However, there were insufficient data to determine if there were significant adverse effects like headaches, dizziness, hypotension and pruritus. B. Dopamine antagonists In 12 studies involving 899 women, we found that dopamine antagonists (both metoclopramide and droperidol) were effective in reducing both intraoperative nausea and vomiting, and postoperative nausea and vomiting. However, there were insufficient data to determine if there were significant adverse effects like headaches, dizziness, hypotension and pruritus. C. Corticosteroids. In six studies involving 490 women, corticosteroids were found to be effective at reducing intraoperative nausea and vomiting. However, we did not identify any benefit for postoperative nausea and vomiting. D. Antihistamines. In three studies involving 365 women, antihistamines were effective at reducing postoperative nausea and vomiting, but none of the studies assessed intraoperative nausea and vomiting. There are no data on possible adverse effects. E. Anticholinergic drugs. In four studies involving 453 women, we found that anticholinergic drugs were effective at reducing intraoperative nausea but not intraoperative vomiting. No study assessed postoperative nausea, however, there was a reduction in postoperative vomiting in one study involving 161 women but there were insufficient data to be sure of other outcomes, including potential</p>	<p>52 studies included, references see article.</p>	

included in a separate review.

adverse effects.

F. Sedatives. In four studies involving 285 women, we found a reduction in intraoperative and postoperative nausea and vomiting. There were insufficient data on potential adverse effects. G. Opioids. There was just one study involving 120 women and this found no difference in postoperative nausea or vomiting. H. Supplemental oxygen. There were two studies involving 294 women and these studies found no difference in our primary outcomes.

J. Intravenous fluids. There was just one small study involving 10 women and this provided insufficient data to be able to report findings with any degree of assurance.

K. Acupressure/acupuncture. In six studies involving 649 women, we found a reduction in intraoperative nausea but we identified no difference in postoperative nausea or intraoperative and postoperative vomiting, although there is likely to be insufficient.

**Author's Conclusion:** This study indicates that many agents, from a diverse range of pharmacological classes, have efficacy in preventing intraoperative and postoperative emetic symptoms at caesarean section. This is perhaps consistent with the multi-factorial pathogenesis of the condition. Of the included interventions, 5 HT3 antagonists, dopamine antagonists and sedatives all showed a reduction in

the majority of our primary outcomes. The other classes of drugs and interventions show effects on some of these outcomes only, for example, acupuncture/acupressure was found to reduce intraoperative nausea, but was not found to affect vomiting or postoperative nausea. This may reflect the amount of data available.

There is little evidence that combinations of treatment are superior to single agents but few studies looked at these aspects. The studies suggest that emetic symptoms are common both during and following caesarean section. Placebo arms of trials included in this review suggest an intraoperative incidence of nausea in the order of 20% to 60%. This gives some weight to published guidelines recommending prophylaxis rather than treatment of emesis at caesarean section (NICE 2011).

## Methodical Notes

### Funding Sources: Internal sources

- The University of Liverpool, UK.

### External sources

- National Institute for Health Research, UK.

NIHR NHS Cochrane Collaboration Programme Grant Scheme award for NHS-prioritised centrally-managed, pregnancy and childbirth systematic reviews: CPGS02

COI: None known.

**Study Quality:** Two review authors independently assessed the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Intervention.

"Studies were mainly small and of unclear quality."

**Heterogeneity:** We assessed statistical heterogeneity in each meta-analysis using the TZ (tau-squared), IZ and ChiZ statistics. We regarded heterogeneity as substantial if the IZ was greater than 30% and either TZ was greater than zero or there was a low P value (less than 0.10) in the ChiZ test for heterogeneity. Where we found heterogeneity and used a random-effects meta-analysis, we reported the average risk ratio, or average mean difference or average standardised mean difference.

**Publication Bias:** Planned but not investigated to low number of included studies for individual outcomes. "Had there been 10 or more studies in a meta-analysis, we would have investigated reporting biases (such as publication bias) using funnel plots."

### Notes:

Oxford level of evidence: 1 systematic review and meta-analysis.

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis Databases: Cochrane Gynaecology and Fertility specialised register, CENTRAL, MEDLINE, Embase, PsycINFO and CINAHL, and trials registers in November 2017. We also checked references, and contacted study authors for additional studies.</p> <p>Search period: Inception - 11.2017</p> <p>Inclusion Criteria: We included randomised controlled trials (RCTs) comparing different methods and administrative protocols for conscious sedation and analgesia during oocyte retrieval.</p> <p>Exclusion Criteria: -</p>	<p>Population: Women undergoing transvaginal oocyte retrieval during IVF treatment.</p> <p>Intervention: 1. Conscious sedation and analgesia versus no treatment or placebo 2. Conscious sedation and analgesia versus different methods such as general and spinal anaesthesia, including acupuncture and paracervical block 3. Different protocols of conscious sedation and analgesia such as patient-controlled or physician-controlled sedation</p> <p>Comparison: see intervention</p>	<p>Primary: 1. Intraoperative pain score, defined as pain reported during or immediately after oocyte retrieval as measured on a visual analogue scale (VAS), a Likert scale, or another defined numerical or non-numerical scale 2. Postoperative pain score, defined as pain reported at some time (minutes or hours) after oocyte retrieval as measured on a VAS, a Likert scale, or another defined numerical or non-numerical scale</p> <p>Secondary: 1. Live birth rate and ongoing pregnancy rate (beyond 20 weeks) per woman 2. Clinical pregnancy rate per woman (established by pregnancy test and confirmed by ultrasound) 3. Fertilisation rate per woman 4. Side effects of analgesia (nausea and vomiting) 5. Postoperative complications (airway, blood pressure, recovery time, spinal headache) 6. Patient satisfaction (women's reports of satisfaction with pain relief and anaesthetic care throughout the oocyte retrieval procedure)</p> <p>Results: Study characteristics: 24 identified randomised controlled trials, involving 3160 women (1545 in control groups and 1615 in intervention groups), comparing the effects of five different methods of conscious sedation and pain relief including general anaesthesia.</p> <p>Results: only guideline relevant outcomes reported, rest see article.</p> <p>Primary outcomes: Postoperative pain <u>CSA plus acupuncture versus CSA plus acupuncture or electroacupuncture</u> Postoperative pain was greater in the CSA plus placebo acupuncture (i.e. CSA without acupuncture) group than in the CSA plus acupuncture group (MD on 0-10 VAS 0.60, 95% CI -0.10 to 1.30; N = 61; very low-quality evidence, Sator-Katzenschlager 2006).</p> <p>This finding was supported by two other studies, which reported binary data, and in which conscious sedation only was associated with more pain at one hour postoperatively when compared with conscious sedation plus electroacupuncture (100/170 (59%) vs 47/146 (32%) reported pain), as well as at two to five hours postoperatively (70/170 (42%) vs 38/146 (26%) reported pain; P &lt; 0.01; N = 316) (Meng 2008). Similarly, conscious sedation plus electroacupuncture was reported to be associated with lower cumulative pain scores than conscious sedation alone (insufficient data details; N = 694) (Meng 2009).</p> <p>CSA versus general anaesthesia CSA was associated with less pain (Likert scale 0 to 3) 30 minutes after completion of the procedure when compared with general anaesthesia (MD on 0 to 3 Likert scale -1.90, 95% CI -2.24 to -1.56; N = 50; very low-quality evidence) (Ben-Shlomo 1999).</p> <p>Secondary outcomes: Side effects of analgesia When investigators compared CSA plus placebo acupuncture versus CSA plus acupuncture, they provided insufficient evidence to show whether there was a difference in the number of women reporting nausea during oocyte retrieval (OR 1.64, 95% CI 0.46 to 5.88; N = 62; very low-quality evidence). Similarly, when comparing CSA plus placebo acupuncture versus conscious sedation plus electroacupuncture, investigators found no clear evidence of differences between groups for this outcome (OR 1.09, 95% CI 0.33 to 3.58; N = 62; very low-quality evidence). Two of 29 women (7%) in the CSA plus placebo group reported nausea and vomiting versus none in the other two groups one hour post treatment (Sator-Katzenschlager 2006).</p>	<p>Ben-Shlomo 1999; Battacharya 1997; Cook 1993; NG 2001; Coskun 2011; Elnabity 2017; Gejervall 2005; Guasch 2005; Gunaydin 2007; Humaidan 2004; Lier 2014; Lok 2002; Ma 2008; Matsota 2012; Meng 2008; Meng 2009; Ocal 2002; Oztruk 2006; Ramsewak 1990; Sator-Katzenschlager 2006; Stener-Victorin 1999; Stener-Victorin 2003; Stener-Victorin 2003; Thompson 2000; Zelcer 1992.</p>

When investigators compared CSA plus placebo acupuncture versus conscious sedation plus electroacupuncture, they found no clear evidence of a difference in reported side effects for nausea and vomiting during oocyte retrieval (17/146 (12%) vs 28/170 (16%) and 3/146 (2%) vs 3/170 (1.8%), respectively; N = 80) nor at one hour postoperatively (13/146 (9%) vs 19/170 (11%) and 4/146 (2.7%) vs 2/170 (1.2%), respectively) nor at two to five hours postoperatively (15/146 (10%) vs 26/170 (15%) and 11/146 (7.5%) vs 15/170 (9%), respectively) (Meng 2008). When comparing CSA with general anaesthetic, researchers found insufficient evidence to show whether there was a difference in postoperative vomiting (OR 0.46, 95% CI 0.08 to 2.75; N = 50) (Ben-Shlomo 1999). In another study, researchers found no evidence of a difference in the number of women experiencing fewer than two episodes of vomiting (0/29 (0%) versus 2/29 (6.9%)), and women experiencing more than two episodes of vomiting (0/29 (0%) versus 0/29 (0%), P = 0.15; respectively) (Matsota 2012).

#### Postoperative complications

When comparing CSA versus general anaesthetic, investigators found no clear evidence of a difference in the rate of airway obstruction (OR 0.14, 95% CI 0.02 to 1.22; N = 58; very low-quality evidence), but fewer women in the conscious sedation group needed mask ventilation (OR 0.05, 95% CI 0.01 to 0.20; N = 58; very low-quality evidence) (Matsota 2012).

**Author's Conclusion:** Evidence does not support one particular method or technique over another for providing effective conscious sedation and analgesia for pain relief during and after oocyte retrieval.

Simultaneous use of sedation combined with analgesia such as the opiates, further enhanced by paracervical block or acupuncture techniques, resulted in better pain relief than was attained by one modality alone. Evidence was insufficient to show conclusively whether any of the interventions provided influenced pregnancy rates. All reviewed techniques were associated with a high degree of patient satisfaction. Women's preferences and resource availability for choice of pain relief merit consideration in practice.

#### Methodical Notes

**Funding Sources:** Internal sources

- None, Other.

External sources

- None, Other.

**COI:** IK, RW and EP have no conflicts to report. SB has received support for travel and accommodation as invited speaker on topics unrelated to the current work.

**Study Quality:** Three review authors (IK, EP, RW) independently assessed each trial for risk of bias according to the Cochrane Handbook for Systematic Reviews of Intervention.

Evidence quality was generally low or very low, mainly owing to poor reporting and imprecision.

**Heterogeneity:** For each meta-analysis, we assessed statistical heterogeneity by using I<sup>2</sup> and Chi<sup>2</sup> statistics. We determined that substantial heterogeneity was present if I<sup>2</sup> was greater.

**Publication Bias:** "We planned to present a funnel plot if publication bias was questionable because some trials had not been identified (Higgins 2011), but no analysis included sufficient studies to warrant this."

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

No obvious methodological flaws.

Lee, A. et al. Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. Cochrane Database of Systematic Reviews. . . 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (59 articles) Databases: Cochrane CENTRAL; OVID MEDLINE; OVID EMBASE; ISI Web of Science; World Health Organization Clinical Trials Registry and ClinicalTrial.gov; reference lists of relevant articles, reviews, and trials.</p> <p>Search period: previous version of the review from <u>2009 - 12/2014</u>.</p> <p>Inclusion Criteria: All randomized trials of techniques that stimulated the PC6 acupoint compared with sham treatment or drug therapy, or combined PC6 acupoint and drug therapy compared to drug therapy, for the prevention of PONV. Interventions used in these trials included acupuncture, electro-acupuncture, transcutaneous electrical acupoint stimulation, transcutaneous nerve stimulation, laser stimulation, capsicum plaster, acu-stimulation device, and acupressure in people undergoing surgery. Primary outcomes were the incidences of nausea and vomiting after surgery. Secondary outcomes were the need for rescue antiemetic therapy and adverse effects.</p> <p>Exclusion Criteria: -</p>	<p>Population: We included all surgical patients without age limitation in the review. The age limits for children were defined by each study. We considered all types of surgery.</p> <p>Intervention: Techniques intended to stimulate the PC6 acupoint: acupuncture, laser acupuncture, transcutaneous electrical stimulation, conventional peripheral nerve stimulation, acustimulation device, acupressure, and capsicum plaster;</p> <p>Comparison: sham treatment or drug therapy</p>	<p>Primary: 1. Incidence of postoperative nausea. 2. Incidence of postoperative vomiting, defined as either retching or vomiting, or both.</p> <p>Secondary: 1. Need for rescue antiemetic drug when prophylaxis failed. 2. Adverse effects from PC6 acupoint stimulation or antiemetic drug, or both.</p> <p>Results: Results: Primary: <u>Incidence of postoperative nausea:</u> 40 trials (n=4742) examined PC6 acupoint stimulation for the prevention of nausea. PC6 acupoint stimulation reduced the incidence of nausea (RR 0.68, 95% CI 0.60 to 0.77) but there was substantial heterogeneity (IR statistic = 67%). As the heterogeneity among trials was substantial and there were study limitations, we downgraded the evidence from high to low quality. Using trial sequential analysis, the required information size and boundary for benefit were reached for nausea. <u>Incidence of postoperative vomiting, defined as either retching or vomiting, or both</u> 45 trials examined PC6 acupoint stimulation for the prevention of vomiting, in 5147 participants. PC6 acupoint stimulation reduced the incidence of vomiting (RR 0.60, 95% CI 0.51 to 0.71) but there was substantial heterogeneity (IR statistic = 64%). Secondary: <u>Need for rescue antiemetic drug when prophylaxis failed:</u> The need for a rescue antiemetic was less after PC6 stimulation compared to sham treatment in 39 trials involving 4622 participants (RR 0.64, 95% CI 0.55 to 0.73). There was moderate heterogeneity (IR statistic = 44%). <u>Adverse effects from PC6 acupoint stimulation and/or antiemetic drug</u> Overall, the side effects associated with PC6 acupoint stimulation were minor and self limiting. There were no side effects for participants receiving acupuncture; electroacupuncture, acupressure; or transcutaneous electro-acupoint stimulation.</p> <p>Author's Conclusion: Implications for practice Given that adverse effects associated with PC6 acupoint stimulation are minor and transient, the number needed to treat for an additional beneficial (NNTB) outcome suggests that P6 acupoint stimulation is worthwhile when the baseline risk of PONV is high (i.e. above 60% as defined by Gan 2014). For example, the NNTB (95% CI) is 5 (4 to 7) for nausea and 4 (3 to 6) for vomiting at baseline risk of 60%. PC6 acupoint stimulation may be considered as an alternative to antiemetics in people in whom exposure is undesirable, for example, pregnant or breast-feeding women, and those with contraindications to antiemetics (Streitberger 2011). We do not have sufficient evidence to determine the effects of multimodal PC6 acupoint stimulation and antiemetic on the prevention of PONV.</p>	<p>59 articles included. For list see full article.</p>

## Methodical Notes

### Funding Sources: Internal sources

- Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong.

### External sources

- 2008 and 2014 Cochrane Complementary Medicine Field Bursary, USA.

This work was partially funded by Grant Number R24 AT001293 from the National Center for Complementary and Alternative Medicine

(NCCAM). The contents of this systematic review are solely the responsibility of the authors and do not necessarily represent the official

views of the NCCAM or the National Institutes of Health.

COI: Anna Lee has no conflicts relating to this review.

Simon KC Chan has no conflicts relating to this review.

Lawrence TY Fan has no conflicts relating to this review.

**Study Quality:** Risk of bias was evaluated for each study in the domains of sequence generation, allocation concealment, blinding of participants, healthcare providers, and outcome assessors, incomplete outcome data, selective outcome reporting, and comparison of baseline characteristics for each group in a 'Risk of bias' table. GRADE approach to describe the overall quality of the outcome, rating it as high, moderate, low or very low.

The quality of evidence was variable, depending on the PC6 acupoint stimulation intervention and comparison group examined. The degree of risk of biases across trials also varied, with few trials (Gan 2004; Xu 2012) rated at low risk of bias.

**Heterogeneity:** We measured heterogeneity using the IR statistic, a measure of the proportion of total variation in the estimates of treatment effect that is due to heterogeneity between studies rather than due to chance. We described the level of heterogeneity as not important (IR statistic from 0% to 40%), moderate (IR statistic from 30% to 60%), substantial (IR statistic from 50% to 90%) and considerable (IR statistic from 75% to 100%).

There was high heterogeneity for some of the outcomes, which also led to the overall body of evidence being downgraded.

**Publication Bias:** We used the contour-enhanced funnel plot to differentiate asymmetry due to publication bias from that due to other factors.

"The contour-enhanced funnel plots for nausea and vomiting showed no evidence of publication bias."

### Notes:

Oxford level of evidence: 1

Overall and study descriptives for individual studies are missing.

Schlüsselfrage:

3.3.2 Effektivität von Analgetika\_Lidocain

Fragestellung wurde 2016 durch IFOM aktualisiert, daher wurde in 2020 nur eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

Inhalt: 4 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Forget, P. 2019	1	Systematic review and meta-analysis and network meta-analysis (24 studies).
Gajjar, K. 2016	1	Systematic review and meta-analysis (19 studies)
Minakaran, N. 2020	1	Systematic review and meta-analysis (13 studies).
Weibel, S. 2018	1	Systematic review and meta-analysis (68 articles)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 4 Bewertung(en)

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level: 1</b></p> <p><b>Study type:</b> Systematic review and meta-analysis and network meta-analysis (24 studies).  <b>Databases:</b> CENTRAL, MEDLINE, Elsevier Embase, and LILACS. Clinical trials.gov. Also clinical trial registries and handsearched the reference lists of trials and review articles.</p> <p><b>Search period:</b> Inception - 25 November 2018.</p> <p><b>Inclusion Criteria:</b> We included randomized and quasi-randomized controlled trials comparing the frequency of TNS after spinal anaesthesia with lidocaine to other local anaesthetics. Studies had to have two or more arms that used distinct local anaesthetics (irrespective of the concentration and baricity of the solution) for spinal anaesthesia in preparation for surgery. We included adults who received spinal anaesthesia and considered all pregnant participants as a subgroup. The follow-up period for TNS was at least</p>	<p><b>Population:</b>                      We included all adults who received spinal anaesthesia. The followup of these participants was at least 24 hours and longer for participants who developed TNS. We chose this time interval because the symptoms of TNS appear within 24 hours after spinal anaesthesia.</p> <p><b>Intervention:</b>                      The included studies had to have two or more arms that used a distinct local anaesthetic (irrespective of the dose, concentration, and baricity of the solution) for spinal anaesthesia in</p>	<p><b>Primary:</b> Presence of any transient neurological symptoms (TNS), defined as pain originating in the gluteal region and radiating to both lower extremities and appearing within up to 24 hours after full recovery (return of sensory and motor function) has been made from uneventful and non-complicated spinal anaesthesia.</p> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• Postoperative neurological symptoms (sensory deficits including numbness and weakness) which lasted longer than 24 hours after onset of spinal anaesthesia and which did not exist before the anaesthetic.</li> <li>• Postoperative neurological signs (motor deficits including weakness in a radicular distribution) which lasted longer than 24 hours after onset of spinal anaesthesia and which did not exist before the anaesthetic.</li> </ul> <p><b>Results: Study population:</b>                      We included 24 studies with 2253 enrolled participants in the NMA. Reported outcomes were available for 2226 participants. There were 27 (1.65%) dropouts, or missing or not reported outcomes. Due to these numbers, we did not perform any related sensitivity analysis.</p> <p><b>Summary of main results</b>  <u>Only summary reported here, du to length, rest see article.</u>                      The main clinical question addressed by this review is whether local anaesthetics used for spinal anaesthesia caused symptoms of TNS less frequently than lidocaine. We included 24 trials of mostly low- to moderate-quality evidence (GRADE), reporting on 2226 participants of whom 239 developed TNS, in the analysis. Included studies mostly had unclear to high risk of bias. Compared with lidocaine, most local anaesthetics were associated with a reduced risk of TNS development (with the exception of 2-chloroprocaine and mepivacaine) (bupivacaine: RR 0.16, 95% CI 0.09 to 0.28; 12 studies; moderate-quality evidence; 2- chloroprocaine: RR 0.09, 95% CI 0.01 to 1.51; 2 studies; low-quality evidence; levobupivacaine: RR 0.13, 95% CI 0.02 to 0.69; 2 studies; 4 studies; very low-quality evidence; prilocaine: RR 0.18,</p>	<p>24 studies included: Ali Hassan 2015, Aouad 2001, Breebart 2003, Casati 2007, de Weert 2000, Etezadi 2013, Fanelli 2009, Gozdemir 2010, Hampl 1995a, Hampl 1998, Hodgson 2000, Imbelloni 2010, Keld 2000, Le Truong 2001, Liguori 1998, Martinez Bourio 1998, Pawlowski 2012, Philipp 2001, Pollock 1996, Pradhan 2010, Salazar 2001, Salmela 1998, Teunkens 2016, Ostgard 2000.</p>

<p>24 hours.</p> <p><b>Exclusion Criteria:</b> We excluded studies dealing with meperidine as a sole intrathecal agent, or combinations of local anaesthetics and opioids. We also excluded studies in which spinal anaesthesia was combined with epidural analgesia to restrict our analysis to intrathecal injection of pure local anaesthetics. This approach was meant to support the clinical and methodological comparability across all direct comparisons in the whole network.</p>	<p>preparation for surgery.</p> <p><b>Comparison:</b> other types of local anaesthetics.</p>	<p>95% CI 0.07 to 0.49; 4 studies; moderate-quality evidence; procaine: RR 0.14, 95% CI 0.04 to 0.52; 2 studies; moderate-quality evidence; ropivacaine: RR 0.10, 95% CI 0.01 to 0.78; 2 studies; low-quality evidence). Approximately one in five participants who received spinal anaesthesia with lidocaine developed TNS. The NMA included 24 studies. These studies assessed eight different local anaesthetics. The number of pair-wise comparisons was 32 and the number of unique pair-wise comparisons was 11. This analysis showed that, compared to lidocaine, the RRs of TNS development were lower for bupivacaine, levobupivacaine, prilocaine, procaine, and ropivacaine with RRs in the range of 0.10 to 0.23 while 2-chloroprocaine and mepivacaine did not differ.</p> <p><b>Author's Conclusion: Implications for practice</b> There is low to moderate-quality evidence that transient neurological symptoms (TNS) are probably less frequent following spinal anaesthesia with bupivacaine, levobupivacaine, prilocaine, procaine, and ropivacaine than with lidocaine. Very-low to low-quality evidence suggests that TNS occurs after 2-chloroprocaine and mepivacaine is used for spinal anaesthesia at a similar frequency with lidocaine, but the evidence is very uncertain.</p> <p>Among the studies included in this review, approximately one in five participants who received spinal anaesthesia with lidocaine developed TNS. This review showed that painful symptoms that are attributed to TNS ceased by the fifth postoperative day in all participants.</p> <p>Finally, the risks of TNS should be weighed against the benefit of rapid, short-acting anaesthesia and the patient's viewpoint must be considered in the decision as to whether to use lidocaine for ambulatory anaesthesia. Globally, the quality of evidence of reported studies is of very low to moderate quality and this should be taken into account when interpreting the results of this review. Finally, the results of one ongoing study (Characteristics of ongoing studies) and two studies in the Studies awaiting classification section may alter the conclusions of the review once assessed.</p>	
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<p><b>Methodical Notes</b></p> <p><b>Funding Sources:</b> none reported.</p> <p><b>COI: PF:</b> none. <b>JAB:</b> none.</p> <p><b>EMT:</b> taught a 'safe sedation simulation' course to doctors and nurses as a consultant for Applied Medical Visualizations.</p> <p><b>NLP:</b> is a tenured professor (University of Utah) and has no conflicts of interest regarding the topic of this review. He has received payment for the development of educational presentations (Barash, Cullen, Toelting Clinical Anaesthesia 8th Edition) and provided consultancy (St Marks Hospital, Salt Lake City, UT; JB3 Bioscience Inc, Salt Lake City, UT; Elute, Salt Lake City, UT) on topics unrelated to the current review.</p> <p>He has received financial supplements to attend Cochrane meetings. He also has stocks and shares in companies who have no interests in the topic of this review (TIAA-CREF, Fidelity, Vanguard, USAA, Morgan Stanley).</p> <p><b>Study Quality:</b> The overall quality of the included RCTs based on risk of bias assessment ranged from unclear to high. All of the studies were randomized; however, 10 studies did not specify the method of randomization (referring to a random number table, computergenerated random number sequence, tossing coin, etc.) and were thus considered to have an unclear risk of bias with regard to randomization of participants.</p> <p><b>Heterogeneity:</b> "We conducted pair-wise meta-analyses for all comparisons of local anaesthetics. We assumed a random-effects model for all data syntheses. We used an inverse variance weighting for summary statistics and random-effects models as we expected methodological and clinical heterogeneity across the included studies resulting in varying effect sizes between studies of pair-wise comparisons. We reported summary statistics as point estimates with 95% CIs; and determined summary statistics to indicate a difference if 95% CIs did not cross the line of identity." Heterogeneity is considered in the overall quality of the body of evidence for the GRADE summary of findings.</p> <p><b>Publication Bias:</b> Publication bias is considered in the overall quality of the body of evidence for the GRADE summary of findings.</p> <p><b>Notes:</b> Oxford level of evidence: 1 Systematic review and meta-analysis.</p>
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Gajjar, K. et al. Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment. Cochrane Database of Systematic Reviews. . . 2016



Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (19 studies)</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase for studies of any design relating to analgesia for colposcopic management. We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.</p> <p>Search period: Inception - 2016</p> <p>Inclusion Criteria: Randomised controlled trials (RCTs) that compared all types of pain relief before, during or after outpatient treatment to the cervix, in women with CIN undergoing loop excision, laser ablation, laser excision or cryosurgery in an outpatient colposcopy clinic setting.</p> <p>Exclusion Criteria: none described.</p>	<p>Population: Women with CIN undergoing loop excision, laser ablation, laser excision or cryosurgery treatment of the cervix in an outpatient colposcopy clinic setting.</p> <p>Intervention: All types of pain relief before, during or after outpatient treatment to the cervix, compared with no pain relief or another type of pain relief. We excluded studies that included treatment performed under general anaesthetic.</p> <p>Comparison: placebo or no treatment</p>	<p>Primary: • Presence or absence of pain, as a dichotomous outcome, or the degree of pain, measured by visual analogue scale (VAS) or categorical scales</p> <p>Secondary: • Speed of procedure (in minutes). • Blood loss (either in millilitres (ml) or categorical scale as none, mild or minimal, heavy, troublesome or as dichotomous data). • Any moderate or severe adverse eGects (dizziness, fainting, shaking, delayed discharge, etc.).</p> <p>Results: Participant characteristics Age of the women in the included trials ranged from 17 to 85, mean age across the trials ranged from 27 to 35 years. Results: only pain relief described here due to length, rest see article Pain relief reported on visual analogue scale 15 trials reported the degree of pain relief during the procedure as VAS. All 19 trials used VAS to assess pain immediately after the procedure. In addition, one trial reported VAS for scoring pain after insertion of speculum, after spray or injection of local anaesthetic solution and 30 minutes after the procedure. The pain scores were further stratified according to the size of the excised loop. Kizer 2014 reported VAS for pain due to injection of local anaesthetic solution and cramping pain after procedure in addition to VAS pain scores immediately after the procedure. Seven trials used a 100- mm or 10-cm linear analogue scale, where 0 was no pain at all and 100 (or 10 in the 10-cm scale) was worst pain imaginable. One trial reported pain relief on 120-mm linear VAS, which was converted to percentages. 3 studies reported pain relief as VAS; however, the values were median and interquartile range (IQR), rather than mean and SD. 2 studies reported VAS on an 11-point scale (0 to 10 or 10-cm scale) where 0 was no pain and 10 was severe pain. Pain relief reported on verbal rating scores 5 trials reported pain relief on verbal rating score (VRS) categorised as none, mild, moderate or severe. Pain relief reported on other categorical scales In addition to VAS, Johnson 1989 and Johnson 1996 reported pain relief as an objective score, given by the attending nurse and laser operator on a categorical scale of 0 to 2. The attending colposcopist of another trial scored pain on a categorical scale (0 = none to 4 = severe) as well as by women undergoing treatment (0 = none to 5 = unbearable) (Howells 2000). The Sarkar 1993 trial measured pain scores for pain relief after treatment and not just during treatment. However, the time scale for carrying out the pain score was not specified. The trial of Al-Kurdi 1985 asked women whether additional analgesics were required within the first 24 hours. Cruickshank 2005 asked women whether additional pain relief was required after treatment. It would appear that this was asked at six months' follow-up, which carries a risk of recall bias. Owing to this risk, we did not include these data in the analysis.</p> <p>Author's Conclusion: Implications for practice Oral analgesia, EMLA cream (benzocaine gel, lignocaine-prilocaine cream), transcutaneous electrical nerve stimulation (TENS), lignocaine spray or benzocaine gel did not provide any benefit in pain relief during cervical colposcopy treatment. Spraying of the cervix with cocaine spray before treatment resulted in better pain relief during the procedure and also less troublesome bleeding. Local anaesthetic agent combined with a vasoconstrictor agent resulted in better pain control compared with placebo and was associated with less blood loss. Buffered injection of lignocaine with adrenaline was not superior to non-buffered lignocaine with adrenaline. Mean observed blood loss score was less with lignocaine plus adrenaline as compared with prilocaine plus felypressin. Direct cervical injection of local anaesthetic with a vasoconstrictor agent resulted in reduction in pain scores during treatment and should be considered for all cervical colposcopy treatment for cervical intraepithelial neoplasia (CIN). However, we could draw no conclusions with regards to optimum number of sites to inject in the cervix, depth of injection in the cervix (superficial, deep, or both) and dose of the agent used. In terms of adverse eGects, combination of prilocaine with felypressin caused fewer adverse eGects than lignocaine with adrenaline. Inhalation of gas mixture in addition to standard pain relief injection appears to have additional pain relief benefit. In routine clinical practice, intracervical injection of analgesic with a vasoconstrictor,</p>	<p>Al-Kurdi 1985, Connel 2000, Crompton 1992, Cruickshank 2005, Diakomanolis 1997, Duncan 2005, Frega 1994, Howells 2000, Johnson 1989, Johnson 1996, Kizer 2014, Lee 1986, Lipscomb 1995, Mikhail 1988, Rogstad 1992, Sammarco 1993, Sarkar 1993, Vanichtanikul 2013, Winters 2009.</p>

particularly those related to vasopressin, appeared to be the optimum analgesia for treatment

**Methodical Notes**

**Funding Sources: Internal sources**

• No sources of support supplied

**External sources**

• Department of Health, UK

NHS Cochrane Collaboration programme Grant Scheme CPG-10/4001/12

COI: KG - none known.

PMH - none known

AB - None known

GO - recipient of a MCRC Clinical Research Training Fellowship, and previously received a Wellbeing of Women Entry Level Scholarship

**Study Quality:** 6 trials were at low risk of bias, as they satisfied at least five of the criteria that we used to assess risk of bias. 9 trials were at moderate risk of bias as they satisfied three or four of the criteria. Five trials confirmed blinding of participants and healthcare professionals, but it was unclear whether the outcome assessor was blinded. Four trials confirmed that participants and/or healthcare professionals were not blinded but did not report whether the outcome assessor was blinded or not. In the trial of Vanichtantikul 2013 comparing a spray with local injection, operator blinding was not possible.

**Heterogeneity:** "We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001), and, when possible, by subgroup analyses. If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons."

**Publication Bias:** "Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects. When there is evidence of small-study effects, publication bias will be considered as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, sensitivity analyses will be performed using fixed effects models."

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Minakaran, N. et al. Topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification cataract surgery in adults. Cochrane Database of Systematic Reviews. . . 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (13 studies). Databases: 1. Cochrane Central Register of Controlled Trials (CENTRAL) 2. MEDLINE (OvidSP) 3. Embase (OvidSP) 4. LILACS BIREME iAH</p> <p>Search period: <u>1980 - 2020</u></p> <p>Inclusion Criteria: We included only randomized controlled trials (RCTs) where participants underwent phacoemulsification for age-related cataract under topical anaesthesia with or without intracameral lidocaine either in two eyes of the same participant, or in different participants. We also included studies that used oral or intravenous sedation in addition to local anaesthesia.</p>	<p>Population: Adult participants only who underwent phacoemulsification for cataract under topical anaesthesia with, or without, intracameral lidocaine.</p> <p>Intervention: We excluded studies that only included low-risk participants and excluded more difficult operative cases, for example people with hard lens nuclei or small pupils. We also excluded studies assessing only participants with Fuchs' endothelial dystrophy.</p> <p>Comparison: Studies involving the administration of topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification.</p>	<p>Primary: 1. Intraoperative pain or discomfort. 2. Postoperative pain or discomfort. 3. Participant satisfaction with anaesthesia.</p> <p>Secondary: 1. Need for additional anaesthesia during surgery. 2. Surgeon satisfaction with operative procedure. 3. Measures relating to possible intraocular toxicity. 4. Intraoperative adverse events (complications) attributable to choice of anaesthesia.</p> <p>Results: Study population: A total of 2388 eyes of 2355 participants were recruited in the included studies. Where specified, the age range of participants was between 34 and 95 years. Results: only postoperative pain (primary outcome) reported here, due to length. Rest see article. <u>2. Postoperative pain or discomfort</u> 5 studies, comprising 811 eyes of 811 participants, measured postoperative pain (Carino 1998; Crandall 1999; Gillow 1999; Joshi 2013; Lofoco 2008). Carino 1998 used a novel 4-point scale, however the other four studies used a 10-point scale and were compatible for metaanalysis (Crandall 1999; Gillow 1999; Joshi 2013; Lofoco 2008). The data derived from these four trials (31% of total studies), comprising 751 eyes of 751 participants (31% of total eyes), did not show any benefit of intracameral lidocaine in addition to topical anaesthesia on postoperative pain (mean difference in pain score was 0.12 points lower in the intracameral lidocaine group; 95% CI -0.29 to 0.05; P = 0.15). There was no heterogeneity between the results of the studies (I<sup>2</sup> = 0%).</p> <p>This result was the same for both the subgroup that did not receive routine sedation (P = 0.25) (Crandall 1999; Gillow</p>	<p>Boulton 2000, Carino 1998, Chuang 2007, Crandall 1999, Gillow 1999, Gills 1997, Hussain 2017, Joshi 2013, Lofoco 2008, Martin 1998, Roberts 2002, Tan 2011, Tseng 1998.</p>

<p><b>Exclusion Criteria:</b> none specified.</p>	<p>We did not place any restrictions on specific topical anaesthetic agent drugs, concentrations, or method of delivery. We did not place any restrictions on concentration of intracameral lidocaine.</p>	<p>1999; Joshi 2013), and the subgroup with routine sedation (P = 0.17) (Lofoco 2008). Using the GRADE approach, we found the quality of the evidence to be moderate. We downgraded by one level due to one of the studies, contributing 51.4% of the weight in the meta-analysis, having a high risk of performance bias as the surgeon was not blinded (Joshi 2013), and due to indirectness of evidence, whereby one trial met the eligibility criteria for inclusion but involved a restricted population of myopic participants only with axial length greater than 26 mm (Lofoco 2008).</p> <p><b>Author's Conclusion: Implications for practice</b> "Our review demonstrates there is moderate-quality evidence that supplementation of topical anaesthesia with intracameral lidocaine (concentration 0.5% to 1%) for phacoemulsification cataract surgery in adults likely reduces participant perception of intraoperative pain or discomfort. Whilst supplemental intracameral lidocaine does reduce the likelihood of the participant experiencing any pain (as opposed to no pain) intraoperatively, the absolute difference in mean pain scores on the 10-point scale is small, and it is not clear whether this is of great clinical significance. Overall, supplementation with intracameral lidocaine probably results in a slight reduction in intraoperative pain perception. Both topical anaesthesia plus intracameral lidocaine, and topical anaesthesia alone, generally had low intraoperative pain scores. As such, both would be acceptable methods of anaesthesia for cataract surgery.</p> <p>Our review does not demonstrate a benefit of supplemental intracameral lidocaine in addition to topical anaesthesia for reduction of postoperative pain (moderate-quality evidence). Evidence was insufficient to determine the impact on participant satisfaction (low-quality evidence) or on the need for additional intraoperative anaesthesia (low-quality evidence).</p> <p>There is moderate-quality evidence that supplementation of topical anaesthesia with intracameral lidocaine likely does not increase measures of intraocular toxicity, specifically loss of corneal endothelial cells. There is low-quality evidence that the incidence of intraoperative adverse events may be unchanged when topical anaesthesia is supplemented with intracameral lidocaine. However, as randomized controlled trials are not the optimum medium for looking at this, this result should be interpreted with caution. Overall, however, the review supports the safety of using intracameral lidocaine in addition to topical anaesthesia."</p>
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#### Methodical Notes

**Funding Sources: Internal sources**  
• Moorfields Eye Hospital NHS Foundation Trust, UK  
**External sources**  
• No sources of support supplied

**COI:** None known.

**Study Quality:** Two review authors (NM, DGE) independently assessed risk of bias in accordance with the tools and methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

**Heterogeneity:** We considered clinical heterogeneity, methodological heterogeneity and statistical heterogeneity by examining study characteristics and forest plots of the results. We used the I<sup>2</sup> statistic to quantify inconsistency across studies, and the Chi<sup>2</sup> test to assess statistical heterogeneity for meta-analysis. We interpreted an I<sup>2</sup> value of 30% or more as moderate, and 50% or more as substantial, as this suggests that more than 50% of the variability in effect estimates was due to heterogeneity rather than sampling error (chance). We considered P < 0.10 to represent significant statistical heterogeneity for the Chi<sup>2</sup> test.

**Publication Bias:** "We planned to create and examine funnel plots to explore possible small-study and publication biases if we were able to pool more than 10 studies. However, this was not the case in this review, therefore we did not create funnel plots."

Using the GRADE approach, we found the quality of the evidence to be moderate. There were no studies with high risk of bias in any domain, no significant heterogeneity, and no evidence of publication bias."

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (68 articles)</p> <p>Databases: 1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1). 2. MEDLINE (Ovid SP, 1966 to 25 January 2017). 3. Embase (Ovid SP, 1980 to 25 January 2017). 4. CINAHL (EBSCO host, 1982 to 25 January 2017).</p> <p>Search period: <u>2014-02/2017.</u></p> <p>Inclusion Criteria: We included randomized controlled trials comparing the effect of continuous perioperative IV lidocaine infusion either with placebo, or no treatment, or with thoracic epidural analgesia (TEA) in adults undergoing elective or urgent surgery under general anaesthesia. The IV lidocaine infusion must have been started intraoperatively, prior to incision, and continued at least until the end of surgery.</p> <p>Exclusion Criteria: participants undergoing: 1. any kind of emergency procedure, and 2. minor surgical procedures, which are sometimes conducted using local or regional anaesthesia alone and do not provide a control event rate being high enough to demonstrate an effect of the investigated intervention.</p>	<p>Population: We included results obtained in adult (over 18 years) participants, independent of sex, undergoing any elective or urgent surgical procedure on any body part(s), and only if the procedure required general anaesthesia.</p> <p>Intervention: We included all studies comparing the effect of continuous perioperative lidocaine infusion, either with no treatment or placebo treatment, or with epidural analgesia. The IV lidocaine infusion must have been started intraoperatively (with or without an IV bolus) prior to incision and continued until the end of surgery. In trials of this intervention, standard care to enhance the postoperative recovery after surgery should also be provided.</p> <p>Comparison: no treatment or placebo</p>	<p>Primary: 1. Pain score at rest (0 to 10 cm, 0 to 100 mm visual analogue scale (VAS), numeric rating scale (NRS)), at 'early', 'intermediate', and 'late time points' 2. Gastrointestinal recovery: postoperative ileus (dichotomous), time to first defaecation/bowel movement (hours), time to first flatus (hours), and time to first bowel sounds (hours) 3. Adverse events (dichotomous; e.g. death, arrhythmias, other heart rate disorders or any sign of lidocaine toxicity)</p> <p>Secondary: Secondary outcomes 1. Length of hospital stay 2. Functional postoperative neuropsychological status scales 3. Surgical complications 4. Patient satisfaction 5. Cessation of the intervention 6. We investigated two separate outcomes for postoperative nausea and vomiting (PONV): First, postoperative nausea including PONV, if nausea was not separately reported in the study (referred to below as 'nausea') and, second, postoperative vomiting, both at 'early time points' (dichotomous; in postanesthesia care unit (PACU)) and 'overall' 7. Intraoperative opioid consumption 8. Postoperative opioid consumption, 'in PACU' and 'overall'</p> <p>Results: Results: <u>Only early time-points postoperative pain described here, due to length:</u> Rest see article. 34 trials that contributed to our meta-analysis used different scores when reporting on postoperative pain. 13 studies asked the participants about pain on a visual analogue scale (VAS) from 0 to 10 cm; in 12 studies a VAS from 0 to 100 mm was used; and in 9 studies the trialists used a numeric rating scale (NRS) from 0 to 10. Pain score at rest, 'early time points' (1 hour to 4 hours postoperatively, or in the PACU) 29 trials reported pain score data at early time points postoperatively (1 to 4 hours, or in the PACU); involving 1656 participants (37% of the total participants included in this review), 829 participants received the intervention and 827 participants received a placebo treatment. The metaanalysis of the early pain score data showed reduced pain ratings in the lidocaine group compared to the control group (SMD -0.50, 95%confidence interval (CI)-0.72 to-0.28; I<sup>2</sup> = 79%; 29 studies, 1656 participants; Analysis 1.1). A SMD of 0.50 fewer in the average pain score of the intervention group is equivalent to an average pain reduction (mean difference (MD)) in the order of 0.37 cm to 2.48 cm on a VAS 0 to 10 cm scale, depending on the variance of the study. However, the 95% prediction intervals (PIs) included both appreciable benefit and harm (95% PI -1.61 to 0.62). In consideration of the high statistical heterogeneity (I<sup>2</sup> = 79%),we performed preplanned subgroup analyses according to the type of surgery (open abdominal, laparoscopic abdominal, other surgery) and the lidocaine infusion dose (infusion dose &lt; 2 mg/kg/h and ≥ 2 mg/kg/h) used in the individual trials. Heterogeneity was not reduced below an I<sup>2</sup> of 50% in any of the subgroups and the tests for subgroup difference did not reach statistical significance . However, the different tau<sup>2</sup>s of the surgical subgroupsmight have contributed to the failure to identify surgical procedures as having different effect estimates (P = 0.017). Exclusion of one outlier study (Saadawy 2010), reduced the I<sup>2</sup> from 79% to 61% and the estimated effect to a SMD of -0.39 with a 95% CI reaching from -0.56 to -0.23. 6 trials reported pain scores as median with interquartile range (IQR). A sensitivity analysis excluding all trials reporting data as median did not affect the overall result of the estimated effect (Table 2).CI but the</p>	<p>68 articles included, see article.</p>

range of true mean effects mostly remained in areas of clinical non-relevance (95% PI -0.60 to 0.38).

The preplanned subgroup analyses on type of surgery and lidocaine regimen (dose and timing) did not explain heterogeneity for all subgroups and tests for subgroup differences did not reach statistical significance (Table 3; Table 4). However, the different tau 2s of the surgical subgroups might have contributed to the failure to identify surgical procedures as having different effect estimates (P = 0.049; Table 5). None of the estimated effects of the different subgroups were of clinical relevance. 4 trials reported pain scores as median with IQR. A sensitivity analysis excluding all trials reporting data as median did not affect the overall result for the estimated effect on pain score at late postoperative time points. For this outcome, we classified 21, five, and 13 trials as high or unclear risk of selection bias, blinding, and attrition bias, respectively; we excluded these trials in the sensitivity metaanalyses. The 95% CIs of all sensitivity analyses remained in areas of clinical non-relevance.

The contour-enhanced funnel plot and the linear regression test suggested funnel plot asymmetry but trim and fill sensitivity analysis (with k = 4 studies added) did not change the conclusion (the 95% CI remained in areas of clinical non-relevance; Table 11). We graded the quality of evidence for the outcome, 'pain score at rest (late time points)' as moderate (we combined the downgrade for study limitations and publication bias by one level); the 95% CIs (main meta-analysis and sensitivity analyses) and the 95% PI were narrow and the range of true mean effects remained in areas of clinical non-relevance, therefore, we did not downgrade for inconsistency and imprecision.

**Author's Conclusion:** We are uncertain whether IV perioperative lidocaine, when compared to placebo or no treatment, has a beneficial impact on pain scores in the early postoperative phase, and on gastrointestinal recovery, postoperative nausea, and opioid consumption. The quality of evidence was limited due to inconsistency, imprecision, and study quality. Lidocaine probably has no clinically relevant effect on pain scores later than 24 hours. Few studies have systematically assessed the incidence of adverse effects. There is a lack of evidence about the effects of IV lidocaine compared with epidural anaesthesia in terms of the optimal dose and timing (including the duration) of the administration. We identified three ongoing studies, and 18 studies are awaiting classification; the results of the review may change when these studies are published and included in the review.

## Methodical Notes

**Funding Sources:** Internal sources  
• Departmental resources only, Germany.  
External sources  
• No sources of support supplied

**COI:** specified, extensive list, see article.

**Study Quality:** Two review authors (independently performed the study quality assessment using a critical appraisal form provided by the Cochrane Anaesthesia, Critical and Emergency Care (ACE) Group with minor modifications. We resolved any disagreements by discussion between the review authors, with a further review author acting as arbiter (original review: PK; update: SW). We assessed the risk of bias of included studies using the Cochrane 'Risk of bias' tool (Higgins 2011). The standard domains include random sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective reporting; and any other bias.

**Heterogeneity:** We assessed the clinical and methodological differences of included studies. We used clinical judgement, not heterogeneity statistics, to decide whether we could combine the studies. We reported statistical heterogeneity using the Chi<sup>2</sup> test and the I<sup>2</sup> statistic. We calculated both for each of the outcomes listed in the 'Types of outcome measures' section. We declared statistical heterogeneity if P < 0.1 for the Chi<sup>2</sup> statistic and I<sup>2</sup> ≥ 30%. We classified heterogeneity following the interpretation specified within the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Briefly, we determined heterogeneity as not important for I<sup>2</sup> of 0% to 40%, as moderate for I<sup>2</sup> of 30% to 60%, as substantial for I<sup>2</sup> of 50% to 90%, and as considerable for I<sup>2</sup> of 75% to 100% (Higgins 2011).

**Publication Bias:** We created contour-enhanced funnel plots as plots of the trial's effect estimates against the precision (inverse of the SE of the estimate) including contour lines corresponding to perceived 'milestones' of statistical significance (P = 0.01, 0.05, 0.1) for outcomes having 10 or more included studies. We used the funnel plot primarily as a visual aid for detecting reporting bias and small-study effects. In addition to funnel plots, we further explored the relation of the treatment effect and study size by regression analysis by method of moments using an arcsine transformation for RR (Rücker 2008), and weighted regression for MD/SMD (Egger 1997). We performed sensitivity analyses by using the trim and fill method to

identify and correct for funnel plot asymmetry arising from publication bias (Duval 2000). We reported the estimated number of missing studies and the adjusted intervention effects derived by performing the meta-analyses, including the filled studies. We performed explorative analyses of reporting bias (funnel plot asymmetry) with the R package 'metasens' (version 0.3-1), an add-on package for 'meta'.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

**Schlüsselfrage:**

**3.3.2 Effektivität von Analgetika\_NOPA**

Fragestellung wurde 2016 durch IFOM aktualisiert, daher wurde in 2020 nur eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

**Inhalt: 6 Literaturstellen**

Literaturstelle	Evidenzlevel	Studientyp
Ahmad, G. 2017	1	Systematic review and meta-analysis. (19 studies)
Galvin, I. M. 2019	1	Systematic review and meta-analysis (43 studies)
Gaskell, H. 2017	1	Systematic review and meta-analysis: 24 studies. To assess the efficacy and safety of single dose oral ketoprofen and oral dexketoprofen compared with placebo for acute postoperative pain, using methods that permit comparison with other analgesics evaluated in the same way, and criteria of efficacy recommended by an in-depth study at the individual patient level.
Hearn, L. 2016	1	Systematic review and meta-analysis (5 studies). To assess the analgesic efficacy and associated adverse events of single dose dipyrone for moderate to severe acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.
McNicol, E. D. 2016	1	Systematic review and meta-analysis (75 studies included) To assess the efficacy and safety of IV formulations of paracetamol for the treatment of postoperative pain in both adults and children.
McNicol, E. D. 2018	1	Systematic review and meta-analysis (7 studies included). To assess the analgesic efficacy and adverse effects of single-dose intravenous diclofenac, compared with placebo or an active comparator, for moderate to severe postoperative pain in adults.

**OXFORD (2011) Appraisal Sheet: Systematic Reviews: 6 Bewertung(en)**

Ahmad, G. et al. Pain relief for outpatient hysteroscopy. Cochrane Database of Systematic Reviews. . . 2017			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis. (19 studies)</p> <p>Databases: Cochrane Gynaecology and Fertility (CGF) Trials Register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL and two trials registers (ClinicalTrials.gov and WHO ICTRP), together with reference checking and contact with study authors and experts.</p> <p>Search period: Inception - September 2016.</p> <p>Inclusion Criteria: We included randomised</p>	<p>Population: Adult (aged over 18 years) women attending for an outpatient hysteroscopy.</p> <p>Intervention: Analgesics (topical or oral) versus placebo or no treatment</p> <p>* Opioids versus placebo or no treatment</p> <p>* Local anaesthetics versus placebo or no treatment</p> <p>* NSAIDs</p>	<p>Primary: Pain score</p> <p>* Pain score during the procedure (validated pain scale)</p> <p>* Pain score after the procedure (validated pain scale): a) within the first 30 minutes of the procedure b) more than 30 minutes after the procedure</p> <p>Secondary: Failure to complete the procedure</p> <p>Adverse effects and complications: nausea, vomiting, constipation, drowsiness, respiratory depression, hypotension, allergic reaction, and infection.</p> <p>Results: Only summary results displayed here, due to length: Our review has shown a beneficial effect of using local anaesthetic compared to placebo during hysteroscopy, within 30 minutes of the procedure and more than 30</p>	<p>Al-Sunaidi 2007, Arnau 2013, Broadbent 1992, Cicinelli 1997, Cicinelli 1998, Clark 1996, Costello 1998, Esteve 2002, Fnikiotis 1992, Giorda 2000, Hassan 2016a, Hassan 2016b, Kabli 2008, Kokanali 2013, Lau 1999, Lau 2000, Lin 2005, Lukes 2015, Makris 2001, Mercorio 2002, Mohammadi 2015, Nagele 1997, Senturk 2016, Sharma 2009, Soriano 2000, Stigliano 1997, Tam 2001, Teran-Alonso 2014, van den Bosch 2011, Vercellini 1994, Wong 2000, Zupi 1995.</p>

controlled trials (RCTs) comparing use of pharmacological interventions with other pharmacological interventions and pharmacological interventions versus placebo or no treatment.

Exclusion Criteria: -

versus placebo or no treatment  
 \* Paracetamol or similar versus placebo or no treatment.  
 • Analgesics (topical or oral or inhaled) versus other analgesics  
 \* Opioids versus paracetamol  
 \* Opioids versus local anaesthetics  
 \* Opioids versus NSAIDs  
 \* Local anaesthetics versus NSAIDs  
 \* NSAIDs versus paracetamol  
 \* Paracetamol versus local anaesthetics (LA)  
 \* Any analgesic versus any other analgesic  
  
 Comparison: see intervention.

minutes after the procedure. However, while this effect is statistically significant, it is too minimal to be clinically significant. There was some evidence of benefit for the use of oral analgesics, both opioids and NSAIDs, but findings were inconsistent and evidence was poor quality. The study of sublingual opioid reported a high rate of nausea and vomiting in the intervention group. Data on other adverse events were scanty and inconclusive. Local anaesthetics were associated with a lower rate of failure to complete the procedure due to pain, but data on failure to proceed due to cervical stenosis did not clearly show a difference.

**Author's Conclusion: Implications for practice**  
 There was no consistent good-quality evidence of a clinically meaningful difference in safety or effectiveness between different types of pain relief compared with each other or with placebo or no treatment in women undergoing outpatient hysteroscopy.

**Methodical Notes**

**Funding Sources:** Internal sources  
 • None, Other.  
 External sources  
 • None, Other.

**COI:** declared, none present.

**Study Quality:** We used the Cochrane 'Risk of bias' tool for assessing risk of bias in each study (Higgins 2011). The domains that we considered were: sequence generation and allocation concealment (selection bias); blinding of personnel, participants and outcome assessors (performance and detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias.  
 We assessed the quality of the evidence using GRADE criteria: risk of bias (with regard to internal validity), consistency of effect, imprecision, indirectness and publication bias). Two review authors working independently made judgements about evidence quality (high, moderate, low or very low), resolving any disagreements by discussion.

**Heterogeneity:** We used four methods to assess heterogeneity.  
 • We performed a ChiV test. If significant, we judged that there would be a strong possibility of high heterogeneity.  
 • We calculated the IV statistic to help determine heterogeneity (Higgins 2003). As a guide, we used the following thresholds (Deeks 2011):  
 \* 0% to 40%: might not be important;  
 \* 30% to 60%: may represent moderate heterogeneity;  
 \* 50% to 90%: may represent substantial heterogeneity;  
 \* 75% to 100%: considerable heterogeneity.  
 • Overlap of the confidence interval of individual trials  
 • Variations in the point estimate of individual trials  
 After considering these four methods we made a judgement on whether there was significant heterogeneity in the meta-analysis, and detailed our reasons in the text.

**Publication Bias:** "We aimed to minimise the potential impact of reporting bias by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. We planned to use a funnel plot to assess publication bias, if there were more than 10 studies in the same analysis (Sterne 2011)."  
 We constructed a funnel plot for analysis 1.1. It did not show any strong suggestion of publication bias."



Notes:  
Oxford level of evidence: 1 Systematic review and meta-analysis.

Galvin, I. M. et al. Pharmacological interventions for the prevention of acute postoperative pain in adults following brain surgery. Cochrane Database of Systematic Reviews. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (43 studies) Databases: MEDLINE, Embase, CINAHL, CENTRAL, Web of Science and two trial registries together with reference checking and citation</p> <p>Search period: Inception - 28th of November 2018.</p> <p>Inclusion Criteria: The objectives are to assess the effectiveness of pharmacological interventions for prevention of acute postoperative pain in adults undergoing brain surgery; compare them in terms of additional analgesic requirements, incidence of chronic headache, sedative effects, length of hospital stay and adverse events; and determine whether these characteristics are different for certain subgroups.</p> <p>Exclusion Criteria: Review articles, observational studies, case reports, case series, non-randomized studies and studies that had no control groups. Studies that investigated the use of agents with analgesic potential for non-analgesic purposes. The rationale for this decision was based on a high likelihood of important differences — in inclusion and exclusion criteria, dosages, timing, ancillary analgesic usage and attributable side effects — between studies that investigated these agents for their analgesic efficacy and studies that investigated them for their nonanalgesic effects. We excluded those undergoing neurosurgical procedures that did not involve accessing the brain such as spinal operations. We excluded interventions that were specifically given for the relief of established acute pain after brain surgery as opposed to those given before pain had become established. We excluded studies which were clearly ineligible (e.g. in vitro studies, animal studies, studies in children, case reports) at this stage.</p>	<p>Population: Adults (defined as more than or equal to 18 years of age at the time of study enrolment), undergoing either supratentorial or infratentorial craniotomy or craniectomy either as an elective or emergency procedure. We excluded those undergoing neurosurgical procedures that did not involve accessing the brain such as spinal operations.</p> <p>Intervention: Any pharmacological drug or pharmacological technique evaluated against a control for the prevention of acute postoperative pain in adults undergoing neurosurgery.</p> <p>Comparison: control</p>	<p>Primary: 1. Mean differences in validated measures of acute postoperative pain intensity measured at the following times: a. anytime in the first six hours postoperatively; b. 12 hours postoperatively c. 24 hours postoperatively; d. 48 hours postoperatively</p> <p>Secondary: 1. Analgesic success as measured by achievement of 'no worse than mild pain' with 'no worse than mild pain' being defined as a score of R 30/100 mm on a visual analogue scale or R 3/10 on a numerical rating scale. 2. Mean difference in additional analgesia requirement at the same time points 3. Mean difference in validated measures of sedation at the same time points. 4. Mean difference in incidence of chronic post-craniotomy headache with chronic post-craniotomy headache being defined as headache persisting three months or more after surgery. 5. Mean difference in length of critical care unit stay. 6. Mean difference in length of hospital stay. 7. Rate of the adverse events in the perioperative period (intraoperatively until four days postoperatively) including, but not confined to, the following: respiratory depression, hypercapnia, elevated intracranial pressure, hypotension, nausea, vomiting, gastrointestinal bleeding, haematoma formation, nerve injury, local anaesthetic toxicity, local or systemic infection and death from any cause.</p> <p>Results: Only summary results displayed here due to length and number of comparisons. Pain intensity <u>NSAIDs:</u> 6 studies (742 participants) in the meta-analysis. <u>0 to 12 hours:</u> The pooled estimate of effect for MD in pain intensity was -1.11 (95% CI -1.64 to -0.58, P &lt; 0.0001), in the first six hours postoperatively and -0.74 (95% CI -1.22 to -0.26, P = 0.02) at 12 hours postoperatively. We judged the quality of the</p>	<p>43 studies included, references see full article.</p>

evidence to be high.

24 to 48 hours:

The pooled estimate of effect for the MD in pain intensity at 24 hours was  $-0.70$  (95% CI  $-1.26$  to  $-0.14$ ,  $P = 0.01$ , Figure 4). Again, we judged the quality of the evidence to be high.

2. Dexmedetomidine

2 studies (128 participants) measuring postoperative pain intensity in the meta-analysis 0 to 12 hours The pooled estimate of effect for the MD in pain intensity was  $-0.89$  (95% CI  $-1.27$  to  $-0.51$ ,  $P < 0.00001$ ), during the first six hours postoperatively and  $-0.81$  (95% CI  $-1.21$  to  $-0.42$ ,  $P = 0.0004$  at 12 hours postoperatively). Evidence of moderate quality.

3. Pregabalin or Gabapentin

Acute postoperative pain intensity in two studies addressed this outcome.

0 to 6 hours

The pooled estimate of effect was a SMD in pain intensity of  $-0.62$  (95% CI  $-0.90$  to  $-0.34$ ,  $P < 0.0001$ , Analysis 3.1). When re-expressed as the mean difference in pain scores, these values were as follows; MD  $-1.15$  (95% CI  $-1.66$  to  $-0.6$ ). The quality of the evidence was downgraded by two levels to a final level of low.

12 hours Only one study reported this outcome, so a pooled estimate of effect was not calculated.

24 hours

The pooled estimate of effect was a SMD in pain intensity of  $-0.78$  (95% CI  $-2.06$  to  $-0.51$ ),  $P = 0.24$ , Analysis 3.2). When re-expressed as the mean difference in pain scores, these values were as follows; MD  $-0.29$  (95% CI  $-0.78$  to  $-0.19$ ). The quality of the evidence was low.

48 hours

The pooled estimate of effect was a SMD in pain intensity of  $-0.02$  (95% CI  $-0.29$  to  $0.26$ ,  $P$  value  $0.91$ , Analysis 3.3). The quality of the evidence was low.

4. Acetaminophen not significant.

5. Scalp infiltration. see article, when high risk of bias were excluded, scalp blocks was effective at 12 hours

6. Scalp blocks

Pain at 12 hours: 8 studies (294 participants) contributed to a pooled estimate of effect for MD in pain intensity of  $-0.95$  (95% CI  $-1.53$  to  $-0.37$ ,  $P = 0.001$ , Analysis 6.3), again in favour of scalp block producing a statistically significant reduction in pain intensity but with the limitation, important unexplained heterogeneity and a small pooled sample size. We judged

the quality of the evidence to be low, because of imprecision due to a small pooled sample size and inconsistency due to unexplained important heterogeneity.

**Summary:**

For the primary outcome of postoperative pain intensity, nonsteroidal anti-inflammatory (NSAIDs) were beneficial up to 24 hours, dexmedetomidine was effective in the first 12 hours and pregabalin or gabapentin were effective in the first six hours after surgery.

When studies with a high risk of bias were excluded, scalp blocks were effective at 12 hours and scalp infiltration at 48 hours but not at earlier time points.

Acetaminophen did not show any benefit.

**Adverse events**

The only significant difference detected was low-quality evidence for a lower risk of nausea and vomiting in those treated with pregabalin or gabapentin.

**Author's Conclusion:  
Implications for practice**

There is high-quality evidence that NSAIDs reduce pain up to 24 hours postoperatively. The evidence for reductions in pain with dexmedetomidine, pregabalin or gabapentin, scalp blocks, and scalp infiltration is less certain and of generally low quality. There is low-quality evidence that scalp blocks and dexmedetomidine may reduce additional analgesics requirements. There is evidence that gabapentin or pregabalin may decrease nausea and vomiting, with the caveat that the total number of events for this comparison was low.

**Methodical Notes**

**Funding Sources: Internal sources**

- None, Canada.

**External sources**

- None, Canada.

COI: see article,

**Study Quality:** Two authors, independently assessed the risk of bias in included studies using Cochrane's tool for assessing risk of bias as described in the Cochrane Handbook of Systematic Reviews for Interventions (Higgins 2011). We resolved any discrepancies by discussion.

16 studies were judged to be at high risk of other sources of bias. These included studies reported in abstract format only where there was an overall lack of information regarding methods and analysis, making it difficult for the reader to judge the rigour of their methodology.

**Heterogeneity:** We assessed clinical heterogeneity by comparing the following factors between studies: participants, setting, surgical techniques, intervention types, timing and dosages, outcomes assessed and ancillary treatments.

We assessed methodological heterogeneity by comparing the risk of bias in the included studies. We assessed statistical heterogeneity by visual inspection of forest plots, the Chi 2 test, and calculation of the I2 statistic. We considered a P value < 0.1 in the Chi 2 test and an I2 statistic > 50% as indicative of significant statistical heterogeneity.

**Publication Bias:** To determine the presence or absence of reporting bias, we planned to examine funnel plots for each meta-analysis that included 10 or more studies to determine the degree of symmetry. However, no meta-analysis in this review

included 10 or more studies. As the majority of studies eligible for inclusion in this review were small studies (typically including fewer than 100 participants), we cannot be confident that publication bias was insignificant. However, by conducting a robust and comprehensive search for all eligible studies and by applying no language restrictions, we hope to have reduced the likelihood of not including studies whose results were not reported in the mainstream literature.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

No overall description of study participants.

Gaskell, H. et al. Single dose oral ketoprofen or dexketoprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. . . 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis: 24 studies. To assess the efficacy and safety of single dose oral ketoprofen and oral dexketoprofen compared with placebo for acute postoperative pain, using methods that permit comparison with other analgesics evaluated in the same way, and criteria of efficacy recommended by an in-depth study at the individual patient level.</p> <p>Databases: For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase. We also searched the reference lists of retrieved studies and reviews, and two online clinical trial registries.</p> <p>Search period: last versio (2009) to 28 March 2017.</p> <p>Inclusion Criteria: Randomised, double-blind, placebo-controlled trials of single dose orally administered ketoprofen or dexketoprofen in adults with moderate to severe acute postoperative pain.</p>	<p>Population: Studies of adults (aged over 15 years) with established postoperative pain of moderate to severe intensity following day surgery or inpatient surgery. For studies using a visual analogue scale (VAS) , we considered that pain intensity of greater than 30 mm equated to pain of at least moderate intensity (Collins 1997).</p> <p>Intervention: Ketoprofen or dexketoprofen, administered as a single oral dose for the relief of acute postoperative pain.</p> <p>Comparison: Placebo</p>	<p>Primary: • Participants achieving at least 50% pain relief over four to six hours after taking the medication.</p> <p>Secondary: • Median (or mean) time to use of rescue medication.</p> <p>• Number of participants using rescue medication over four to six hours after taking the medication.</p> <p>• Number of participants with: any adverse event; any serious adverse event (as reported in the study); withdrawal due to an adverse event, at the end of the (single dose) study period.</p> <p>• Other withdrawals: withdrawals for reasons other than lack of efficacy (participants using rescue medication) or an adverse event at the end of the (single dose) study period.</p> <p>Results: Only summary results described here, due to length.</p> <p>Included studies: In all 24 included studies, the total number of participants who took medication was 5220, of whom 1084 received ketoprofen alone (dose range 6.25 mg to 150 mg; mostly 25 mg and 50 mg), 1120 received dexketoprofen alone (dose range 5 mg to 100 mg; mostly 12.5 mg and 25 mg), and 1156 received placebo.</p> <p>Ketoprofen: vs placebo For ketoprofen 50 mg, 66% of participants in comparisons with placebo were in dental studies and 34% in other types of surgery. Dental studies gave a distinct dose response relationship, with an NNT of 2.4 at 12.5 mg improving to 1.6 at 100 mg for at least 50% pain relief compared with placebo. There was much less of a dose response relationship when all studies were combined, with NNT values between 2.0 and 2.9. The highest (worst) NNT was with the standard oral dose of ketoprofen 50 mg, where the NNT was 2.9 (95% CI 2.4 to 3.7; 8 studies, 594 participants). There was a distinct and statistically significant (P &lt; 0.00006) difference at ketoprofen 50 mg between dental surgery (NNT 1.8 (95% CI 1.5 to 2.2); 3 studies 190 participants) and other surgery (NNT 4.2 (95% CI 3.0 to 6.7); 5 studies, 404 participants).</p> <p>Dexketoprofen: vs placebo For dexketoprofen 25 mg, 38% of participants in comparisons with placebo were in dental studies and 62% in other types of surgery. Dental studies gave a sensible dose-response relationship with anNNT of 3.6 at 10/12.5mg improving to 2.7 at 100mg for at least 50% pain relief compared with placebo. A dose response relationship could not be ascertained for other types of surgery, but NNTvalueswere high, at above 5 for both doses. As a consequence of the larger proportion of participants having had other types of surgery, there was no dose response relationship with all studies together, with NNT values of 3.9 and 4.1 for 10 mg or 12.5 mg and 20 mg or 25 mg, respectively. There was a distinct and statistically significant (P &lt; 0.00006) difference at dexketoprofen 25 mg between dental surgery (NNT 2.7 (95% CI 2.2 to 3.3); 5 studies; 444 participants) and other surgery (NNT 5.7 (95% CI 4.1 to 9.6); 3 studies; 733 participants). Demonstrating a dose response relationship can be difficult except by using a method involving pooling of direct comparison studies (McQuay 2007).</p>	<p>Akural 2009, Arnold 1990, Balzanelli 1996, Cooper 1984, Cooper 1998, Gay 1996, Harrison 1996, Jackson 2004, McGurk 1998, McQuay 2016, Mehlisch 1984, Moore 2015c, Moore 2016, Olson 1999, Olson 2001, Schreiber 1996, Seymour 1996, Seymour 2000, Sunshine 1993, Sunshine 1998, Turek 1988, Vidal 1999.</p>

**Exclusion Criteria:**

-

**Comparison of Ketoprofen und Dexketoprofen:**

The same problems with small numbers and indirect comparisons affected comparisons of doses of ketoprofen and dexketoprofen, where similar efficacy would be expected for dexketoprofen at half the dose of ketoprofen. The amount of information available was inadequate to exclude that there is a 2:1 dose ratio between ketoprofen and dexketoprofen for the same effect in acute pain. This was not found, though in another review, a direct comparison on very limited numbers across different pain models did find the expected result (Moore 2008c). Results for different pain models were clearly heterogeneous in this data set, as Figure 4 and Figure 6 show, comparing dental, postsurgical, and bunionectomy studies. There were too few studies to make any sensible cross-comparisons about effects of different pain models on analgesic efficacy estimates. Where comparison of surgery type has been possible previously, no major effect of pain model has been found, although absolute response rates do differ (Barden 2004; Moore 1998). While third molar extraction studies typically involved participants in their 20s, other types of surgery involved older adults, often in their 40s to 70s. Age might be an issue: data sets in this analysis had many more non-dental surgery studies than is usual, as third-molar extraction typically amounts to around 80% of studies and participants in single dose studies (Moore 2015a). In addition, it is not entirely clear whether the effects of the duration of fasting before drug administration might have been responsible for these results, as food has been shown to affect NSAID absorption (Moore 2014).

**Summary:**

Overall, the results for ketoprofen and dexketoprofen are those expected for NSAID drugs in acute postoperative pain in participants with established pain of at least moderate intensity. NNTs for at least 50% pain relief for ketoprofen and dexketoprofen were generally between 2 and 3 in dental studies, comparable with other commonly used analgesics at recommended doses (e.g. ibuprofen 400 mg: NNT 2.3, Derry 2009a; diclofenac 50 mg: NNT 2.7, Derry 2009b). Median time to use of rescue medication was also comparable at four to five hours. Efficacy appears to be a little better than with paracetamol 1000 mg (NNT 3.2, Toms 2008), and worse than with etoricoxib 120 mg (NNT 1.6, Clarke 2014). In these single dose studies, adverse events did not differ from placebo at any dose of ketoprofen and dexketoprofen, and there were no serious adverse events reported. Withdrawals due to adverse events were uncommon and also did not differ from placebo. This is similar to what is usually found in this type of single dose study (Moore 2015b).

**Author's Conclusion: For people with acute pain**

A single oral dose of ketoprofen 50 mg or dexketoprofen 25 mg provided good levels of pain relief to more people than placebo. Experience has shown that efficacy demonstrated in one acute pain condition is generally applicable in others, although the absolute response rate may vary. Lower doses can also provide good pain relief, but typically to fewer people.

**For clinicians**

A single oral dose of ketoprofen 50 mg or dexketoprofen 25 mg provided good levels of pain relief to more people than placebo. The magnitude of the effect is similar to other good analgesics, as reported in Cochrane Reviews of individual analgesics and in two overviews. Adverse event rates were low, and similar to placebo.

**For policy makers**

Ketoprofen 50mg or dexketoprofen 25mg is an effective analgesic in acute pain.

**Methodical Notes****Funding Sources: Internal sources**

- Oxford Pain Research Funds, UK.

**External sources**

- NHS Cochrane Collaboration Programme Grant Scheme, UK.
- NIHR Biomedical Research Centre Programme, UK.

COI: extensive list, see article.

**Study Quality:** We completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in ReviewManager 5 (RevMan 2014), and assessed criteria for inclusion using the Oxford Quality Score Oxford quality scores were high, with four studies scoring 3/5, 13 scoring 4/5, and seven scoring 5/5. These high scores are indicative of low risk of bias.

**Quality of the evidence**

We used the GRADE system to assess the quality of the evidence related to the key outcomes listed in Types of outcome measures, as appropriate (Appendix 2). Two review authors (HG, SD) independently rated the quality of each outcome.

**Heterogeneity:** We examined heterogeneity using L'Abbé plots (L'Abbé 1987), a visual method for assessing differences in results of individual studies, and using the I2 statistic.

**Publication Bias:** We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher in this condition; Moore 2008b).

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Hearn, L. et al. Single dose dipyrone (metamizole) for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. . . 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> Systematic review and meta-analysis (5 studies). To assess the analgesic eFicacy and associated adverse events of single dose dipyrone for moderate to severe acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes. Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and LILACS; the Oxford Pain Relief Database; two clinical trial registries; and the reference lists of articles.</p> <p><b>Search period:</b> Inception - August 2015</p> <p><b>Inclusion Criteria:</b> We included randomised, double-blind,</p>	<p><b>Population:</b> Studies of adults (aged 15 years or older) with established postoperative pain of moderate to severe intensity following day surgery or inpatient surgery. For studies using a visual analogue scale (VAS), we assumed that pain intensity of greater than 30/100 mm equated to pain of at least moderate intensity (Collins 1997).</p> <p><b>Intervention:</b> Dipyrone, administered as a single dose, compared with matched placebo, administered postoperatively for pain relief. Where studies also included an active comparator, we extracted data for direct comparison. We included oral, rectal, IV, and IM routes of administration.</p> <p><b>Comparison:</b> matched placebo.</p>	<p><b>Primary:</b> Participants achieving at least 50% pain relief over a four to six hour period.</p> <p><b>Secondary:</b> Median (or mean) time to use of rescue medication.</p> <ul style="list-style-type: none"> <li>• Number of participants using rescue medication.</li> <li>• Number of participants with: any adverse event; any serious adverse event (as reported in the study); withdrawal due to an adverse event.</li> <li>• Other withdrawals: withdrawals for reasons other than lack of efficacy (participants using rescue medication).</li> </ul> <p><b>Results:</b> <u>Only summary results displayed due to length, rest see article.</u></p> <p><b>Study overview:</b> This review found 8 studies using various doses of dipyrone (500 to 2000 mg) administered by different routes (oral or IM) and following different surgical procedures, with comparisons to placebo and a variety of active comparators.</p> <p><b>Results:</b> For the primary outcome of at least 50% pain relief over four to six hours, there were sufficient data from placebo-controlled comparisons to analyse only oral dipyrone 500 mg versus placebo (288 participants). The RR was 2.4 (95% CI 1.8 to 3.1), and the NNT was 2.4 (1.9 to 3.2). For every five people treated, two would experience at least 50% pain relief who would not have done so with placebo (moderate quality data). For the same comparison (248 participants), the RR for needing rescue medication within four to six hours was 0.21 (95% CI 0.11 to 0.40), and the NNTp was 3.6 (2.7 to 5.4) (low quality data). For every seven people treated, two would not need rescue medication who would have done with placebo. There was very little information on the mean or median time to use of rescue medication, a useful indicator of the duration of analgesia. Reporting of adverse events was inconsistent, with few events reported, and no analysis was possible. The studies reported no serious adverse events or adverse event withdrawals. Results from studies using different doses and routes of administration were all consistent with a benefit of dipyrone over placebo, but based on very few data. For active-controlled comparisons, there were insufficient data for analysis. Indirect comparisons of NNTs for at least 50% pain relief over four to six hours in reviews of other analgesics using identical methods indicate that dipyrone has similar efficacy to standard ibuprofen 400 mg (NNT 2.5 (2.4 to 2.6)), diclofenac potassium (NNT 2.1 (1.9 to 2.5)), and ketoprofen 12.5 mg (NNT 2.4 (1.9 to 3.1)) (Moore 2015a).</p> <p><b>Author's Conclusion:</b> For clinicians Dipyrone 500 mg taken by mouth provides good pain relief for about 7 in 10 people. We found little evidence for other doses or other routes of administration. This analysis was based on information from relatively few participants and the quantitative estimates were not robust; the results should be interpreted with caution. Use of dipyrone is banned or restricted in many countries because it has been associated with serious blood dyscrasias,</p>	<p>Bhounsule 1990, Boraks 1987, De Miguel Rivero 1997, Dos Santos Pereira 1986, Olson 1999, Pinto 1984, Rubinstein 1986, Sakata 1986.</p>

placebo-controlled trials of single dose dipyrrone for relief of established moderate to severe postoperative pain in adults. We accepted oral, rectal, intramuscular, and intravenous routes of administration.

**Exclusion**

- Criteria:**
- Review articles, case reports, and clinical observations.
  - Studies of experimental pain.
  - Studies where pain relief was assessed only by clinicians, nurses, or carers (ie not participant-reported).
  - Studies of less than four hours' duration or studies that did not present data over a four to six hour period post dose.

particularly agranulocytosis. Susceptibility to these adverse effects may vary between different populations, and the single dose studies used in this review are inadequate to assess adverse events. While dipyrrone may provide adequate analgesia, patients should be monitored for blood dyscrasias as recommended by the manufacturers, if resources allow. The short onset of agranulocytosis seen in case reports is cause for concern. In many countries, other drugs for which more evidence exists are readily available, while in other countries, dipyrrone may be one of only a few drugs available.

**Methodical Notes**

**Funding Sources: Internal sources**

- Oxford Pain Relief Trust, UK.

**General institutional support**

**External sources**

- No sources of support supplied

**COI:** Extensive list declared, see article.

**Study Quality:** We also completed a 'Risk of bias' table, using methods adapted from those described by the Cochrane Pregnancy and Childbirth Group. Two review authors independently assessed risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Chapter 8.5, Higgins 2011), and resolved any disagreements by discussion.

We have used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system to assess the quality of the evidence related to the key outcomes listed in Types of outcome measures, as appropriate. Two review authors independently rated the quality of evidence for each outcome.

GRADE quality of evidence was moderate (At least 50% of maximum pain relief over 4 to 6 h) and low (Participants remedicating within 4 to 6 h).

**Heterogeneity:** We examined heterogeneity visually using L'Abbé plots (L'Abbé 1987), which is a visual method for assessing differences in results of individual studies, and using the I2 statistic.

Heterogeneity was low in the main analysis.

**Publication Bias:** We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (NNT of 10 or higher in this condition) (Moore 2008).

**Notes:**

Oxford level of evidence: 1

McNicol, E. D. et al. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. Cochrane Database of Systematic Reviews. . . 2016

Evidence

level/Study P - I - C

Outcomes/Results

Literature

Types			References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (75 studies included) To assess the efficacy and safety of IV formulations of paracetamol for the treatment of postoperative pain in both adults and children.</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, a clinical trials registry, and reference lists of reviews for randomized controlled trials (RCTs) in any language and we retrieved articles.</p> <p>Search period: previous version (2010) - 02.2016.</p> <p>Inclusion Criteria: Randomized, double-blind, placebo- or active-controlled single dose clinical trials of IV paracetamol or IV propacetamol for acute postoperative pain in adults or children.</p> <p>Exclusion Criteria: pain assessments that were not patient-reported; time periods that were not within those specified in our inclusion criteria; propacetamol being administered intramuscularly; IV paracetamol being administered via a continuous infusion; absence of pain or analgesic outcomes; comparisons of procedures rather than interventions; pre-emptive administration of intervention or administration more than 30 minutes before the end of surgery; non-randomization; all arms receiving IV paracetamol/IV propacetamol; or control groups not receiving either an active control or placebo.</p>	<p>Population: We included studies that evaluated children or adults with postoperative pain following any kind of surgery, including dental, who were able to self report pain intensity or pain relief.</p> <p>Intervention: Intravenous paracetamol or IV propacetamol for postoperative pain relief. The interventions had to be administered within the last 30 minutes before the end of surgery (i.e., not preoperatively or at induction of anesthesia), in the immediate postoperative period or at any time within the first three postoperative days.</p> <p>Comparison: Control interventions, either placebo or another analgesic (e.g., NSAIDs or opioids) Control interventions were subject to the same inclusion and exclusion criteria as for paracetamol and propacetamol; other than that they could be administered via any route.</p>	<p>Primary: 1. Pain relief: number of participants experiencing at least 50% of maximum pain relief over four or six hours postintervention. 2. Pain intensity: we extracted mean pain intensity over both the four- and six-hour postintervention periods in each treatment arm and their corresponding standard deviations (SD), and in turn calculated the mean pain difference between groups.</p> <p>Secondary: 1. Time to achieve 50% pain relief 2. Number of participants requiring rescue medication 3. Time to rescue medication 4. Opioid consumption 5. Patients' global evaluation of therapy 6. Adverse events (AEs)</p> <p>Results: <u>Only summary results displayed, due to length. Rest see article.</u></p> <p>Primary outcomes As in our previous analysis, meta-analyses demonstrate that IV paracetamol and IV propacetamol are statistically superior to placebo for the outcome of the proportion of participants achieving at least 50% pain relief over four or six hours. Estimates of the minimum reduction in acute pain intensity that patients describe as meaningful vary between 30% and 50%, with larger absolute reductions required when baseline pain is more severe. Similar to the original review, the proportion of participants with at least 50% pain relief appears to decrease at six hours in both active groups (and in the placebo groups). Over four hours, 31%, 40%, and 36% of participants receiving IV paracetamol, IV propacetamol, or overall, respectively, had at least 50% pain relief versus 16% in those receiving placebo. Inspection of forest plots suggests low to moderate heterogeneity exists amongst the placebo-controlled studies, quantified by the I<sup>2</sup> statistic of 51% (P value = 0.00001) and 43% (P value = 0.0003) at 4 and 6 hours, respectively; however heterogeneity was lower than in the original review. Heterogeneity may, in part, be explained by the different types of surgeries performed. Placebo rates in dental surgery have been shown to be lower than in other types of surgery (Gray 2005). In the four studies included in our primary analysis that employed the dental model, placebo rates were indeed very low, with the exception of the study by Van Aken and colleagues. Efficacy was also affected by study design. Five studies enrolled participants on the first postoperative day and allowed them to use patient-controlled analgesia (PCA). One study administered the intervention without requiring that the patient report moderate-to-severe pain (Koppert 2006). All other studies were started at first report of moderate-to-severe pain and participants had to request rescue analgesia (Hynes 2006 also enrolled participants on the first postoperative day, but participants had to request analgesia). Sensitivity analysis, with these studies removed, suggests that IV paracetamol and/or propacetamol may have greater efficacy when administered on the day of surgery. When assessing the clinical significance of the above findings, it is possible to indirectly compare the NNT for a single dose of IV paracetamol and/or IV propacetamol with that of a single dose of other analgesics (Bandolier 2010). In this update, the NNTs for combined IV paracetamol and IV propacetamol data (5 at four hours, 6 at six hours) are similar to those seen with various single doses of oral paracetamol (Toms 2008), but inferior to most orally or parenterally administered opioids. While these indirect comparisons are not surprising, the data should be interpreted with caution. The efficacy of the other analgesics in this 'league table' is measured over four to six hours, rather than discretely at four and six hours as we performed in our analyses. As demonstrated above, NNTs may increase (i.e., analgesia diminishes) if measured over six hours in drugs with a short duration of effect. Although NNTs for IV and oral paracetamol are similar, the studies included in each analysis would almost certainly have enrolled different populations. First, participants in the oral studies would have to be capable of taking oral medication immediately postoperatively. Oral administration of medications postoperatively is frequently problematic in that participants may be nauseated or vomiting or may have absorption issues,</p>	<p>75 studies included (36 from original review, 39 from update), for list see article</p>



such as postoperative ileus. Second, participants in the oral studies may have had lower baseline pain. When baseline pain is low, a smaller absolute reduction in intensity is required to effect a clinically important change (Cepeda 2003). For direct comparisons versus other analgesics, the combined analysis of IV paracetamol or propacetamol versus NSAIDs at six hours showed statistical superiority of NSAIDs. However, these data were highly susceptible to publication bias and we assessed the quality of evidence as very low according to GRADE. Mean pain intensity at four and six hours was not presented in the original review because no studies reported these data. For this update, no studies utilizing propacetamol contributed data to pain intensity at either time point. We assessed the data as being of low to very low quality. Comparisons of IV paracetamol versus placebo demonstrated no difference at four hours and statistically significant, but clinically minor reductions in pain at six hours. This may be a consequence of availability of rescue medication. Comparison of IV paracetamol with NSAIDs showed statistical superiority of NSAIDs at both time points, although differences were minor. Analyses exhibited moderate heterogeneity quantified by the I<sup>2</sup> statistic of 58% and 54% at four and six hours, respectively.

**Author's Conclusion: For clinicians**

Our meta-analysis includes high to very low quality evidence that IV paracetamol and IV propacetamol provide superior analgesia in comparison to placebo. Neither IV paracetamol nor IV propacetamol were clinically superior for any efficacy outcome versus other analgesic agents, such as nonsteroidal antiinflammatory drugs (NSAIDs) or opioids. Given alone, they are unlikely to provide sufficient analgesia after surgeries that produce moderate-to-severe pain. If used in combination with opioids they reduce opioid consumption, but this reduction does not appear sufficient to reduce opioid-induced adverse effects (AEs). Both offer an advantage over oral paracetamol due to their faster onset of action and in that many patients are unable to tolerate oral medication postsurgically. Intravenous paracetamol may prove a better option versus IV propacetamol as reconstitution is not required and because the incidence of pain on infusion is reduced.

**For policy makers**

The availability of either IV paracetamol or IV propacetamol varies by country. The decision to add either formulation to a hospital formulary should take into account how adding one would affect current policies for analgesic algorithms, additional workload, and patient satisfaction.

**Methodical Notes**

**Funding Sources: Internal sources**  
 • Saltonstall Fund for Pain Research, USA.  
**External sources**  
 • No sources of support supplied

**COI: EM:** none known.

**MF:** none known. Prior to initial planning and conception of this review update, the institution at which MF is employed received payment for fee-for-service activities from Mallinckrodt Pharmaceuticals, which produces paracetamol/acetaminophen.

**SH:** none known.

**DC:** none known.

**RS:** none known.

**Study Quality:** "Two review authors independently assessed the risk of bias of all included studies in this review using a domain-based evaluation, outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011)."

No overall summary of study risk of bias described.

"We assessed the overall quality of the evidence for each outcome using the GRADE system (GRADEpro GDT 2015), and presented this in the 'Summary of findings' tables. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes."

"When assessing the quality of findings using GRADE, we ranked quality from very low to high across the different efficacy outcomes."

**Heterogeneity:** We assessed statistical heterogeneity by visually examining forest plots and quantified it by using the I<sup>2</sup> statistic. The I<sup>2</sup> statistic is a reliable and robust test to quantify heterogeneity, since it does not depend on the number of trials or on the between-study variance. I<sup>2</sup> measures the extent of inconsistency among studies' results, and can be interpreted as the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. An I<sup>2</sup> value of greater than 50% is considered to indicate substantial heterogeneity (Deeks 2011).

**Publication Bias:** To assess the impact of reporting bias we considered the number of additional participants needed in

studies with zero effect (relative benefit of one) required to change the NNT for all statistically significant outcomes to an unacceptably high level (in this case the arbitrary NNT of 10) (Moore 2008). Where this number was less than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we considered the results to be susceptible to publication bias and therefore unreliable (low quality evidence). We also attempted to mitigate the potential for publication bias by searching the website [http:// www.clinicaltrials.gov](http://www.clinicaltrials.gov) and by contacting the manufacturer of IV paracetamol for an internal reference list of completed studies.

"To assess for publication bias, we calculated the number of additional participants needed in studies with zero effect to increase the NNT for at least 50% pain relief to 10 or greater, which is what we considered to be clinically insignificant (Moore 2008). If the number of additional participants required was less than 400, we considered the result to be susceptible to publication bias. We established through these calculations that our analysis of IV propacetamol versus placebo for the number of participants with > 50% pain relief at six hours was susceptible to publication bias. "

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Notes: High heterogeneity in the main analysis, which is due to differences in operations.

Publication bias discussed, but not shown.

**McNicol, E. D. et al. Single-dose intravenous diclofenac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. . . 2018**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> Systematic review and meta-analysis (7 studies included). To assess the analgesic efficacy and adverse effects of single-dose intravenous diclofenac, compared with placebo or an active comparator, for moderate to severe postoperative pain in adults. Databases: Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online), MEDLINE, and Embase. We checked clinical trials registers and reference lists of retrieved articles for additional studies.</p> <p><b>Search period:</b> Inception - 22 May 2018.</p> <p><b>Inclusion Criteria:</b> We included randomized trials that</p>	<p><b>Population:</b> Adults (aged 18 years and above) with established postoperative pain of moderate to severe intensity following day surgery or inpatient surgery. For studies using a visual analogue scale (VAS), we considered that pain intensity of greater than 30 mm equates to pain of at least moderate intensity (Collins 1997).</p> <p><b>Intervention:</b> Diclofenac, administered as a single IV dose, for the relief of acute postoperative pain.</p> <p><b>Comparison:</b> Placebo or any active comparator.</p>	<p><b>Primary:</b> Participants achieving at least 50% pain relief over a four- to six hour period.</p> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• Median (or mean) time to use of rescue medication.</li> <li>• Number of participants using rescue medication over a four- to six-hour period.</li> <li>• Withdrawals due to lack of eBicacy, AEs, and for any cause.</li> <li>• Participants experiencing any AE.</li> <li>• Participants experiencing any serious AE (SAE). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is lifethreatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardize the patient, or may require an intervention to prevent one of the above characteristics or consequences.</li> <li>• Specific AEs, particularly renal dysfunction, cardiovascular events, bleeding, and thrombophlebitis.</li> </ul> <p><b>Results:</b> Only summary results reported, due to length.</p> <p><b>Study overview:</b> We included 7 studies for inclusion in this review. Study designs were similar, in that most required participants to report moderate to severe pain postoperatively before being assigned to one of the planned intervention groups. Most were single-dose studies that measured pain relief or pain intensity difference after an intervention was administered. Doses of diclofenac varied among studies, although the most commonly employed dose was 75 mg, that is the dose used in clinical practice.</p> <p><b>Efficacy</b> Analysis of our primary outcome, participants achieving at least 50% maximum pain relief, demonstrated that diclofenac was superior to placebo and similar to other NSAIDs. Analysis of lowdose versus higher-dose diclofenac did not demonstrate a doseresponse effect, although this was based on data from only two studies. The relative benefit of diclofenac compared with placebo over four hours was 2.8 (95% CI 2.0 to 4.0). Almost three times as many participants achieved at least 50% pain relief in the diclofenac group compared with those receiving placebo. The NNTB for one additional participant to benefit compared with placebo was 2.4 (95% CI 1.9 to 3.1), which indirectly compares favorably with oral analgesics used in the same setting (Moore 2011b), and similarly to 20 mg of parenteral parecoxib, the only other parenteral NSAID to be analyzed in a Cochrane Review of postoperative pain (Lloyd 2009).</p> <p>The relative benefit at six hours was slightly less (RR 1.8, 95% CI 1.4 to 2.2), suggesting that the analgesic effect of diclofenac starts to decline after four hours. Parenteral diclofenac also demonstrated lower (i.e. superior) NNTBs at four and six hours versus those found in a Cochrane Review of parenteral formulations of paracetamol (acetaminophen) for postoperative pain, where NNTBs were 5 and 6 at four and six hours, respectively (McNicol 2016). Direct comparison of diclofenac with other NSAIDs within this review suggested similar eBicacy (RR 0.94, 95% CI 0.83 to 1.06), but subgroup analysis where</p>	<p>7 articles included. Christensen 2011, Gan 2011, Garcia 1997, Leeson 2007, Maroo 2013, Seymour 2000, Sneyd 2007, Steffen 1994.</p>

compared a single postoperative dose of intravenous diclofenac with placebo or another active treatment, for treating acute postoperative pain in adults following any surgery.

**Exclusion Criteria:**

review articles, case reports, and clinical observations;  
 • studies of experimental pain;  
 • studies of less than four hours' duration or studies that did not present data over four to six hours postdose;  
 • studies where pain was not patient-reported.

a lower dose of 18.75 mg of diclofenac was compared with parenteral ketorolac demonstrated statistical inferiority (RR 0.78, 95% CI 0.65 to 0.93), suggesting that lower doses may be less effective.

For secondary efficacy outcomes, median time to remedication was longer, and the number of participants requesting rescue analgesia was lower (NNTp 3.0, 95% CI 2.2 to 4.5) in those receiving diclofenac versus those receiving placebo. There were insufficient data to analyze these outcomes in head-to-head comparisons with another NSAID. Lastly, there were insufficient data to perform pooled analyses of the number of participants withdrawing from a trial due to lack of efficacy.

**Safety**

Total AE rates were very similar to those with placebo and with other NSAIDs. There was a lack of data for our planned analyses of specific AEs associated with NSAID use, that is renal dysfunction, cardiovascular events, and bleeding, as well as for thrombophlebitis, a recognized issue with parenteral diclofenac use. This no doubt reflects the relative infrequency with which these events occur, particularly in studies of short duration. Limited data from two studies that compared rates of thrombophlebitis with newer formulations of diclofenac versus traditional formulations suggest that rates are lower with newer formulations (Leeson 2007; Maroo 2013). Data from the one study that compared rates of bleeding with diclofenac versus ketorolac did not show a difference, therefore the hypothesis that the balanced COX-1/COX-2 profile of diclofenac results in a reduced rate of bleeding versus the COX-1 specific ketorolac was not confirmed in this review (Gan 2012).

**Author's Conclusion: For adults with moderate to severe postoperative pain:**

The amount and quality of evidence for the use of diclofenac for treating postoperative pain is low. The evidence we have indicates that postoperative administration of diclofenac offers good pain relief for the majority of patients, but further research may impact this estimate. Adverse events appear to occur at a similar rate to other non-steroidal anti-inflammatory drugs (NSAIDs), but information is insufficient to assess whether diclofenac has a different rate of bleeding, renal dysfunction, or cardiovascular events when compared with other NSAIDs. We have insufficient information to confirm that newer formulations of diclofenac are more effective and safer than traditional formulations

**For clinicians**

The amount and quality of evidence for the use of diclofenac for treating postoperative pain is low. The evidence we have indicates that postoperative administration of diclofenac offers good pain relief for the majority of patients, but further research may impact this estimate. Adverse events appear to occur at a similar rate to other NSAIDs, but information is insufficient to assess whether diclofenac has a different rate of bleeding, renal dysfunction, or cardiovascular events when compared with other NSAIDs. We have insufficient information to confirm that newer formulations of diclofenac are more effective and safer than traditional formulations.

**Methodical Notes**

**Funding Sources:** Internal sources  
 • Saltonstall Fund for Pain Research, USA.  
 • Oxford Pain Relief Trust, UK.

**External sources**  
 • No sources of support supplied

**COI:** Ewan D McNicol (EM): none known. EM is a pharmacist with a Master's degree in Pain Research, Education and Policy, and manages patients with acute pain.

McKenzie Ferguson (MF): none known.

Roman Schumann (RS): none known. RS is an anesthesiologist whose practice includes acute perioperative pain management.

**Study Quality:** Two review authors independently assessed risk of bias for each study, using applicable criteria outlined in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in Review Manager 5 (RevMan 2014).

**Heterogeneity:** We assessed statistical heterogeneity by visually examining forest plots and quantified it using the I<sup>2</sup> statistic. The I<sup>2</sup> statistic is a reliable and robust test to quantify heterogeneity, since it does not depend on the number of trials or on the between-study variance. I<sup>2</sup> measures the extent of inconsistency among studies' results, and can be interpreted as the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. An I<sup>2</sup> value of greater than 50% is considered to indicate substantial heterogeneity (Deeks 2011).

**Publication Bias:** To assess the impact of reporting bias we considered the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the NNTB for all statistically significant outcomes to an

unacceptably high level (in this case the arbitrary NNTB of 10). Where this number was less than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we considered the results to be susceptible to publication bias and therefore unreliable (low-quality evidence).

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Overall quality of evidence for all outcomes was considered either low or very low, limiting the possible implications.

**Schlüsselfrage:**

**XX\_3.3.2 vs Placebo**

**Führt bei Erwachsenen postoperativ (P) die Gabe von (Opioiden, Ketamin, Gabapentinoide, evt. A2-Antag.) (I) im Vergleich zu Placebo zu einer verbesserten Analgesiequalität (O: VAS/Morphinverbrauch/Opioid-induzierte Nebenwirkungen)? bzw. zu substantiellen Vorteilen?**

**Inhalt: 45 Literaturstellen**

Literaturstelle	Evidenzlevel	Studientyp
Achuthan, S. 2015	1	Systematic Review and Meta-Analysis of RCTs (17 trials) Hence the present analysis was performed to define the role of gabapentin as a preventive therapy
Brinck, E. C. 2018	1	Systematic Review and Meta-Analysis of RCTs (130 studies with 8341 participants) To evaluate the efficacy and safety of perioperative intravenous ketamine in adult patients for the prevention of acute pain following general anaesthesia.
Fabritius, M. L. 2016	1	SR and META (135 studies)
Felder, L. 2019	1	SR and META (of 6 RCTs)
Frauenknecht, J. 2019	1	Systematic review and meta-analysis (23 studies) This meta-analysis investigated whether opioid-inclusive, compared with opioid-free anaesthesia, without increasing the rate of postoperative nausea and vomiting.
Galvin, I. M. 2019	1	Cochrane Review (43 studies)
Gehling, M. 2009	2	Systematic review and meta-analysis Intrathecal morphine is often used for postoperative analgesia after surgery. We performed a detailed analysis on the frequency of side-effects in patients receiving intrathecal morphine anaesthesia compared with placebo treated patients.
Grant, M. C. 2016	1	Systematic review and meta-analysis (23 studies) The effect of preoperative pregabalin on postoperative nausea and vomiting (PONV).
Hamilton, T. W. 2016	1	SR and META (of 12 RCTs)
Han, C. 2017	1	SR and META (of 7 RCTs)
Han, C. 2017	1	SR and META (of 10 RCTs)
Hu, J. 2018	1	Network META analysis (79 RCTs)
Jessen Lundorf, L. 2016	1	SR
Jiang, H. L. 2017	1	SR and META (of 10 RCTs)
Jiang, Y. 2018	1	SR and Meta-analysis from RCTs (n=9)
Jouguelet-Lacoste, J. 2015	2	Systematic Review of RCTs (29 trials) The aim of this article is to review the evidence associated with giving low-dose IV infusion of ketamine during the period for acute pain.
Le Bot, A. 2015	1	SR and META (of 18 studies)
Li, C. 2017	1	SR and META (5 studies)
Li, F. 2017	1	SR and META (of 7 RCTs)
Li, S. 2017	1	SR and META (of 12 RCTs)
Li, Y. Z. 2019	1	SR and META (of 22 studies)
Li, Z. 2019	1	Systematic Review and Meta-Analysis of RCTs (6 trials, 244 patients) To examine the analgesic efficacy and safety of ketamine after total knee arthroplasty.
Liu, B. 2017	1	SR and META (of 12 RCTs)

Mao, Y. 2016	1	Systematic Review and Meta-Analysis of RCTs (7 trials, 769 patients) The purpose of this systematic review and meta-analysis of randomised controlled trials (RCTs) was to evaluate the effect of gabapentin or pregabalin administration versus placebo after total hip arthroplasty (THA).
Mishriky, B. M. 2015	1	Systematic Review and Meta-Analysis of RCTs (55 trials, 4155 patients) Therefore, we performed this systematic review to provide an updated meta-analysis of the impact of pregabalin on postoperative pain scores and opioid consumption and investigate whether those outcomes are affected by pregabalin dose, frequency of administration, type of anaesthesia, or type of surgery. Secondary objectives were to evaluate the impact of pregabalin administration on anxiety scores and persistent pain, and provide an updated meta-analysis of the effects of pregabalin administration.
Pan, L. 2019	1	Systematic Review and Meta-Analysis of RCTs (7 RCTs, 300 patients) To compare the efficacy of ketamine supplementation versus placebo for knee arthroscopy.
Paramasivan, A. 2020	1	SR and META (24 RCTs included)
Pendi, A. 2018	1	Systematic Review and Meta-Analysis of RCTs (14 trials, 649 patients) To evaluate the effectiveness of perioperative supplemental ketamine to reduce postoperative pain following spine surgery.
Rai, A. S. 2017	1	SR and META (of 4 RCTs)
Ren, Y. 2019	1	Systematic review and meta-analysis: 5 studies "To evaluate effects of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia."
Riddell, J. M. 2019	1	Systematic Review and Meta-Analysis of RCTs (20 trials, 1271 patients) The objective of this systematic review was to critically appraise the evidence from RCTs that evaluate the effectiveness of gabapentin in patients undergoing pain orthopaedic procedures.
Sanchez Munoz, M. C. 2017	1	SR and META (16 trials for quantitative analysis).
Sanders, J. G. 2016	1	Systematic review (15 studies) To identify whether sufficient evidence exists for the routine use of gabapentin in the perioperative setting.
Sun, R. 2014	2	SR and META (7 studies).
Tsaousi, G. G. 2018	1	SR and META (15 studies, whereas only 8 were included in the qualitative analysis)
Ul-Huda, A. 2019	1	SR and META (4 trials)
Viscusi, E. R. 2016	5	Systematic review and meta-analysis (7 studies) To evaluate whether the efficacy and safety profile of fentanyl iontophoretic transdermal systems is similar in geriatric (>=65 years) and non-geriatric (<65 years) patients.
Wang, J. 2020	1	Systematic Review and Meta-Analysis of RCTs (20 trials) The present meta-analysis aimed to evaluate the clinical efficacy of ketamine versus control in reducing postoperative pain and analgesia.
Wang, L. 2017	1	Systematic Review and Meta-Analysis of RCTs (9 trials) The purpose of the current meta-analysis was to determine whether preoperative treatment with ketamine could reduce postoperative pain scores, total morphine consumption, and postoperative nausea and vomiting after cholecystectomy.
Wang, X. 2018	1	Systematic Review and Meta-Analysis of RCTs (40 trials) Thus, we conducted this systematic review and meta-analysis of randomized controlled trials for the treatment of acute postoperative pain.
Wang, Y. M. 2017	1	Systematic Review and Meta-Analysis of RCTs (10 trials, 1207 patients) To determine the efficacy and safety of the preoperative use of pregabalin to treat acute pain after hysterectomy.
Xu, B. 2019	1	Systematic Review and Meta-Analysis of RCTs (10 trials)
Ye, F. 2017	1	Systematic Review and Meta-Analysis of RCTs (5 trials, 212 patients) To assess the efficacy and safety of ketamine for reducing pain and narcotic use for patients undergoing orthopedic surgery.
Zhong, W. G. 2015	1	Systematic Review and Meta-Analysis of RCTs (11 trials, 692 patients) This meta-analysis was conducted to evaluate the efficacy of dexmedetomidine on PONV after general anesthesia.
Zou, Z. 2016	1	Systematic review and meta-analysis (28 studies) To evaluate the relative effects on pain relief and adverse events of intravenous morphine given for pain compared with placebo, other analgesics (local anaesthetics, non-steroidal anti-inflammatory drugs), and other routes of morphine administration.

Achuthan, S. et al. Gabapentin prophylaxis for postoperative nausea and vomiting in abdominal surgeries: a quantitative randomized controlled clinical trials. *Br J Anaesth.* 114. 588-97. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (17 trials) Hence the present analysis was performed to define the role of gabapentin as a preventive therapy for PONV Databases: Medline, Embase and the Cochrane library.</p> <p>Search period: Not described</p> <p>Inclusion Criteria: The criteria for inclusion were (i) patients undergoing abdominal surgery (open or laparoscopic) under general anaesthesia, (ii) preoperative administration of gabapentin irrespective of dose and timing of the dose with respect to surgery, and (iii) trials reporting nausea, vomiting, postoperative nausea and vomiting, or a proportion of patients requiring rescue anti-emetic medication irrespective of the objective of evaluation were included in the final analysis.</p> <p>Exclusion Criteria: Trials evaluating postoperative dosing alone or in addition to preoperative gabapentin were excluded from the final analysis.</p>	<p>Population: Patients undergoing abdominal surgery (open or laparoscopic) under general anaesthesia</p> <p>Intervention: Preoperative administration of gabapentin irrespective of dose and timing of the dose with respect to surgery</p> <p>Comparison: Placebo</p>	<p>Primary: Postoperative nausea, vomiting, composite nausea and vomiting (PONV, as some studies had reported composite outcome of nausea and vomiting), and the proportion of patients requiring rescue anti-emetic medication.</p> <p>Secondary:</p> <p>Results: <u>Results:</u> Only summary results are displayed here. The pooled relative risk (RR), estimated using the random effects model of the metafor package for R, was 0.76 (95% 0.58–0.98) for nausea, 0.62 (0.45–0.85) for vomiting, 0.6 (0.39–1.28) for data represented as composite POI (possibly biased by a single study, as observed in the sensitivity analysis), and 0.6 (0.41 –0.89) for rescue antiemetic use. There was a significant RR reduction for nausea and vomiting when propofol was not used for induction and/or maintenance for anaesthesia. In the abdominal hysterectomy subgroup, there was a significant RR reduction for vomiting but not for nausea.</p> <p>Author's Conclusion: The present analysis provides evidence supporting preoperative gabapentin as pharmacotherapy for prevention of PONV in patients undergoing abdominal surgeries. Future studies comparing preoperative gabapentin with 5HT3 antagonists are needed to precisely define its role in PONV.</p>

#### Methodical Notes

Funding Sources: Not stated.

COI: None.

Study Quality: The methodological quality of the included studies was assessed using the Downs and Black score. Overall the quality was high as reported by the authors.

Heterogeneity: Heterogeneity was assessed based on the calculated I<sup>2</sup> (the proportion of total variability explained by heterogeneity) using the restricted maximum likelihood-based method. I<sup>2</sup> was 94% and the test for heterogeneity was significant (P,0.0001) for PONV.

Publication Bias: The Galbraith plot showed no evidence of publication bias (Supplementary Figure 8). The Egger's test for asymmetry was not significant (P=0.27). T

#### Notes:

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (17 trials)

Substantial heterogeneity was present for PONV

Search period was not described

Publication bias was approximately not present.

Brinck, E. C. et al. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database Syst Rev*

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (130 studies with 8341 participants) To evaluate the efficacy and safety of</p>	<p>Population: Adults aged 18 years and above undergoing a surgical procedure under general anaesthesia.</p> <p>Intervention: People treated intravenously</p>	<p>Primary: Our primary outcome for studies using PCA or opioid as rescue medication was the consumption of opioids in milligrams of morphine equivalents for up to 48 hours after surgery (opioids being the exclusive analgesics used in the included studies). Our primary outcome was also the intensity assessed by means of subjective pain scales in studies not assessing or using PCA, and the absence of opioid rescue medication.</p> <p>Secondary: Time from end of surgery to first request for analgesia or first trigger of PCA, Assessment of postoperative hyperalgesia in the units used in the original studies (e.g. hyperalgesia area under the curve of the surgical wound in square centimetres), Major and minor adverse events, as judged by the investigators, such as hallucinations, nightmares, dizziness, blurred vision, sedation, nausea and vomiting</p> <p>Results: <u>Results:</u> Due to length only summary results are displayed here. We included 130 studies with 8341 participants. Ketamine was given to 4588 participants and</p>

<p>perioperative intravenous ketamine in adult patients when used for the treatment or prevention of acute pain following general anaesthesia.</p> <p>Databases: Cochrane Central Register of Controlled Trials, MEDLINE (via Ovid), Embase (via Ovid)</p> <p>Search period: Inception to July 2018</p> <p>Inclusion Criteria: We included randomised, prospective, double-blind studies in which participants received ketamine alone or placebo alone as a study drug; ketamine was administered in addition to a basic analgesic such as opioid or NSAID in one study group, and compared with a group receiving the same basic analgesic (but without ketamine) in another group; pain intensity, use of opioids, or time to first opioid request were reported outcomes; the minimum size was 10 participants per arm who completed the study.</p> <p>Exclusion Criteria: We did not include short abstracts (e.g. meeting reports).</p>	<p>with ketamine (racemic ketamine or S-ketamine), during general anaesthesia as a bolus dose or as a continuous infusion or, if administered in the postoperative period, via a patient-controlled analgesia device (PCA) or as a continuous intravenous infusion.</p> <p>Ketamine alone or ketamine was administered in addition to a basic analgesic such as opioid or NSAID.</p> <p>Comparison: Placebo alone or group receiving the same basic analgesic (but without ketamine) in another group</p>	<p>participants served as controls. Types of surgery included ear, nose or throat surgery, wisdom extraction, thoracotomy, lumbar fusion surgery, microdiscectomy, hip joint replacement surgery, joint replacement surgery, anterior cruciate ligament repair, knee arthroscopy, mast haemorrhoidectomy, abdominal surgery, radical prostatectomy, thyroid surgery, elective caesarean section, and laparoscopic surgery. Racemic ketamine bolus doses were predominantly 0.25 mg, and infusions 2 to 5 µg/kg/minute; 10 studies used only S-ketamine and one only R-ketamine. Risk of bias was generally low or uncertain, except for study size; most had fewer than 50 participants in the treatment arm, resulting in high heterogeneity, as expected, for most analyses. We did not stratify the main analysis by type of surgery or any other factor, such as dose or timing of ketamine administration, and used a non-stratified analysis. Perioperative intravenous ketamine reduced postoperative opioid consumption over 24 hours by 8 mg morphine equivalents (95% CI 6 to 10 mg; 6 studies, 42 participants) compared with placebo, moderate-quality evidence; 65 studies, 5004 participants). Over 48 hours, opioid consumption was 13 mg lower (95% CI 10 to 15 mg; 19% lower than placebo, moderate-quality evidence; 37 studies, 2449 participants). Perioperative intravenous ketamine reduced pain at rest at 24 hours by 5/100 mm on a visual analogue scale (95% CI 4 to 6 mm lower from 26/100 mm with placebo, high-quality evidence; 82 studies, 5004 participants), and at 48 hours by 5/100 mm (95% CI 3 to 7; 22% lower from 23/100 mm, high-quality evidence; 49 studies, 3333 participants). Pain during movement was reduced at 24 hours (6/100 mm, 14% lower from 42/100 mm, moderate-quality evidence; 29 studies, 1806 participants), and 48 hours (6/100 mm, 16% lower from 42/100 mm, low-quality evidence; 23 studies, 1353 participants). Results for primary outcomes were consistent when analysed by pain at rest or on movement, operation type, and timing of ketamine administration, or sensitivity to study size and pain intensity. No analysis by dose was possible as there was no difference when nitrous oxide was used. We downgraded the quality of the evidence because the numbers of participants were large but small-study effects were present, or twice if numbers were small and small-study effects likely but testing not possible. Ketamine increased the time to first postoperative analgesic request by 54 minutes (95% CI 37 to 71 minutes), from a mean of 39 minutes with placebo (moderate-quality evidence; 31 studies, 1678 participants). Ketamine reduced the time to first postoperative hyperalgesia by 7 cm<sup>2</sup> (95% CI -11.9 to -2.2), compared with placebo (very low quality evidence; 7 studies, 333 participants). We downgraded the quality of evidence because of small-study effects or because the number of participants was below 400. CNS adverse events occurred in 187/3600 participants receiving ketamine and 122/2924 (4%) receiving control treatment experienced an adverse event (RR 1.2, 95% CI 0.95 to 1.4; high-quality evidence; 105 studies, 6538 participants). Ketamine reduced postoperative nausea and vomiting from 27% with placebo to 23% with ketamine (RR 0.85, 95% CI 0.81 to 0.96; the number needed to treat to prevent one episode of postoperative nausea and vomiting with perioperative intravenous ketamine administration was 24 (95% CI 16 to 54; high quality evidence; 95 studies, 5965 participants).</p> <p>Author's Conclusion: Perioperative intravenous ketamine probably reduces postoperative analgesic consumption and pain intensity. Results were consistent in different operation types or timing of ketamine administration, with larger and smaller studies, and by higher and lower pain intensity. Postoperative adverse events were little different with ketamine or control. Perioperative intravenous ketamine probably reduces postoperative nausea and vomiting by a small extent, of arguable clinical relevance.</p>
<p><b>Methodical Notes</b></p>		
<p>Funding Sources: None.</p>		
<p>COI: ECVB: none known. ECVB is a specialist physician in anaesthesiology and intensive care medicine and she treats</p>		



postoperative pain.

ET: none known. ET is a specialist physician in anaesthesiology and intensive care medicine and she treats patients suffering from MH: none known. MH is a specialist physician in anaesthesiology and he treats patients with acute postoperative and chronic pain. RFB: none known. RFB is a specialist pain physician (retired).

SS's institution (University of Alberta), received fees for his contribution to an advisory board from Daiichi Sankyo, Inc. (2015). SS is a medicine physician and some of the patients he assesses have painful conditions.

RAM has received grant support from Grünenthal relating to individual patient-level analyses of trial data regarding tapentadol (2015), and Novartis for a network meta-analysis on acute postoperative pain using data from Cochrane Reviews. He has served on boards with RB on understanding pharmacokinetics of drug uptake (2015). He has received honoraria from Omega Pharma (2016) providing advice on trial and data analysis methods.

VK: none known. VK is a specialist physician in anaesthesiology and intensive care medicine and he treats patients suffering from

**Study Quality:** Two review authors (ECVB and ET), independently assessed risk of bias for each study, using the criteria outlined in the Systematic Reviews of Interventions (Higgins 2017), and adapted from those used by the Cochrane Pregnancy and Childbirth Review Group (RAM, ECVB and VKK), independently rated the quality of the evidence for each outcome using the GRADE system, and the guidance of the Cochrane Handbook for Systematic Reviews of Interventions.

Risk of bias was generally low or uncertain, except for study size; most had fewer than 50 participants per treatment arm, results were not expected, for most analyses.

**Heterogeneity:** Two review authors (ECVB and ET), independently assessed the clinical homogeneity of the studies. In case of doubt, a third review author (VK). We used the I<sup>2</sup> statistic, as described in the Cochrane Handbook for Systematic Reviews of Interventions and reported heterogeneity as appropriate.

**Publication Bias:** Publication bias was investigated

**Notes:**

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis (130 studies, 8341 participants)

Risk of bias was generally low or uncertain, except for study size; most had fewer than 50 participants per treatment arm

Substantial heterogeneity was present in most analyses.

Fabritius, M. L. et al. Gabapentin for post-operative pain management - a systematic review with meta-analyses and meta-regression. *Anaesthesiol Scand.* **60.** 1188-208. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR and META (135 studies) Databases: Cochrane Library's CENTRAL, PubMed, EMBASE and Science Citation Index Expanded databases. Reference lists of previous reviews and Google Scholar. <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>; <a href="http://www.controlled-trials.com">www.controlled-trials.com</a>; <a href="http://www.centerwatch.com">www.centerwatch.com</a>; <a href="http://www.eudraCT.com">www.eudraCT.com</a>; and at the homepage of the US Food and Drug Administration (FDA).</p> <p>Search period: The electronic search was last updated 12 April 2016.</p> <p>Inclusion Criteria: Randomized clinical trials investigating perioperative gabapentin intervention vs. placebo or an active placebo group mimicking the sedative effect of gabapentin. Language was not a restriction. Prospective observational and quasirandomized trials were included for evaluation of harm and detection of rare serious adverse events but not for benefit. In addition they are not included in any of the meta-analyses of outcomes. Trials were included regardless of dosage, administration intervals, duration of treatment, or type of surgery.</p> <p>Exclusion Criteria: Trials of non-surgical pain conditions, experimental pain models, chronic pain conditions, or different analgesic co-interventions in compared groups.</p>	<p>Population: The study population included surgical patients of 18 years or above who received gabapentin for post-operative pain.</p> <p>Intervention: Perioperative gabapentin</p> <p>Comparison: Placebo or an active placebo group mimicking the sedative effect of gabapentin.</p>	<p>Primary: 24-h post-operative opioid consumption and incidence of adverse events (SAE). All opioids were converted to intravenous morphine based upon equivalency. Various scales were used to report pain intensity in the trials. All pain intensity scales reporting pain levels were converted to the Visual Analog Scale (VAS) 0 to 100 mm.</p> <p>Secondary: Pain at rest and during mobilization at 6 and 24 hours post-operatively, opioid-related adverse effects, and all other adverse events.</p> <p>Results: In total 9498 (range 20-306) patients were included in the meta-analysis. Gabapentin treatment ranged from 100 to 1200 mg in trials with low risk of bias (n = 96), and from 900 to 2400 mg/day in trials with high risk of bias (n = 36). Initiation of gabapentin treatment varied from 30 minutes to 24 hours post-operatively.</p> <p>Opioid consumption (trials with low risk of bias, n=13): Reduction in 24-h post-operative morphine consumption 95% CI 0.5, 5.6; P &lt; 0.02; I<sup>2</sup> = 90%; 13 trials; 1362 patients (low).</p> <p>Add-on effect (trials with low risk of bias): The predefined subgroup analysis of gabapentin as add-on to another non-opioid analgesic regimen indicated a mean morphine consumption of 1.2 mg (REM: 95% CI 0.3, 2.6; P &lt; 0.05; 1194 patients).</p> <p>Serious adverse events (trials with low risk of reporting bias): The RR of SAE of patients treated with gabapentin vs. placebo was 0.91 (REM: 95% CI 0.91, 2.86; P &lt; 0.10; I<sup>2</sup> = 0%; nine trials, 1014 patients (low)).</p> <p>Pain (trials with low risk of bias): At 6-h post-operatively, pain at rest was not significantly different between groups. At 24-h post-operatively, pain at rest nor pain during mobilization was significantly reduced.</p> <p>Adverse events: (trials with low risk of bias) Risk of nausea, vomiting, sedation, and risk of dizziness were not significantly different between groups.</p>

**Author's Conclusion:** Based on GRADE assessment outcomes in trials with low risk of bias, the results are low of evidence due to imprecision, inconsistency, and in indirectness. Firm evidence for use of gabapentin is lacking. The relevant beneficial effect of gabapentin may be absent and especially when added to multimodal analgesia.

**Methodical Notes**

**Funding Sources:** The project was supported by departmental funding from the Department of Anaesthesiology, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet and Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Rigshospitalet.

**COI:** All authors have completed the ICMJE disclosure form available upon request from corresponding author. VK reports Janssen-Cilag, MSD, Mundipharma, Orion, Pfizer and Steripolar outside of the submitted work. JW reports that he is a member of the Copenhagen Trial Unit to develop the software and manual for doing trial sequential analysis (TSA). AG, PLP, MSH, LN, KH, JBD, OM, and MI have no conflicts to declare.

**Study Quality:** The included trials were assessed for risk of bias according to the Cochrane Handbook. If one or more domains were at high risk of bias, the trial was classified as overall high risk of bias. When one or more domains were categorized as unclear, trials were added to the meta-analyses and subgroup analyses as we aimed for estimates based on the trials with reliable low risk of bias. Predefined subgroup analyses were calculated investigating the risk of bias in low vs. unclear risk of bias.  
 Overall low risk of bias: 16 trials  
 Overall high risk of bias: 77 trials  
 Overall unclear risk of bias: 39 trials.

**Small trial effect:** of the included studies  
 119 trials <50 participants = small trials  
 13 trials < 50 patients in each group and only  
 4 trails included more than 200 patients in each group.

**Heterogeneity:** We examined the heterogeneity between trials using chi-squared test. The heterogeneity was measured by I<sup>2</sup> and D<sup>2</sup> for information size adjustments.

**Publication Bias:** n.a.

**Notes:**  
 CEBM Level of Evidence (Oxford): EL 1 (SR of randomized controlled trials).

**Notes:**  
 Die in dieser Studie eingeschlossenen Artikel überschneiden sich stark mit der Studie von Hu et al. 2018. Da sich die Auswertemodalitäten und Schlussfolgerungen unterscheiden, wurden beide Studien eingeschlossen.

**Anmerkungen für die hier vorliegende Studie:**  
 - zunächst werden 135 Studien eingeschlossen. Für die letztendliche Auswertung werden dann jedoch nur Studien mit niedrigem Risiko für Verzerrung berücksichtigt, was dazu führt, dass mehr als zwei Drittel der Studien in der Ergebnisbetrachtung nicht berücksichtigt werden.  
 - in der Conclusion und einem "Editorial comment" weisen die Autoren deutlich darauf hin, dass die methodische Qualität der eingeschlossenen Studien gering ist (bias Risiko in der Mehrheit der Studien unklar oder hoch, Heterogenität hoch, Mehrheit der eingeschlossenen Studien mit niedrigem Risiko für Verzerrung, Relevanz daher auch als niedrig einzustufen ist).

Felder, L. et al. Perioperative gabapentin and post cesarean pain control: A systematic review and meta-analysis of randomized controlled trials. *J Obstet Gynecol Reprod Biol.* **233.** 98-106. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR and META (of 6 RCTs)</p> <p>Databases: MEDLINE, Ovid, ClinicalTrials.gov, Sciencedirect, the Cochrane Library at the CENTRAL Register of Controlled Trials. No restrictions for language or geographic location were applied.</p> <p>Search period: Inception until October 2018.</p> <p>Inclusion Criteria: RCTs, examining the effect of perioperative gabapentin, women with singleton</p>	<p>Population: Healthy women (ASA I or II) undergoing cesarean delivery at term under spinal anesthesia.</p> <p>Intervention: Patients receiving at least one dose of gabapentin (all trials used 600 mg oral gabapentin) 1 h (in 5/6 trials) before surgery and in one study gabapentin was continued postoperatively for 48 h.</p> <p>Comparison: Either placebo or no treatment.</p> <p>Both gabapentin and placebo groups received the same intrathecal opioids in each study.</p>	<p>Primary: VAS pain score on movement postoperative.</p> <p>Secondary: VAS pain scores at other time points, rest or on movement following surgery, use of intraoperative pain medications or supplemental pain control satisfaction, persistent pain at 24 h postoperative, maternal side effects, and neonatal outcomes.</p> <p>Results: Total of 320 women in the intervention group and 321 women in the control group.</p> <p>VAS pain score was assessed in four trials (n=177 in the intervention group, n=177 control group). With 600 mg oral gabapentin prior to cesarean delivery, women in the intervention group had lower VAS pain scores at 24 h postoperative.</p>

<p>gestations received spinal anesthesia and underwent cesarean delivery at term (37weeks).</p> <p>Exclusion Criteria: Trials including multiple gestations, preterm delivery, general anesthesia, studies comparing gabapentin to another drug, and quasi-randomized trials.</p>	<p>Immediate postoperative medications used in both groups were an NSAID, usually ketorolac or diclofenac, as well as acetaminophen.</p>	<p>on movement compared to those who received (36.4 vs 43.7, MD -11.60, 95% CI -23.03 to -0.16). <u>VAS pain scores at rest or on movement</u> at 12 and 24 h postoperative points showed no significant differences. <u>Additional pain medications or supplemental analgesics</u> showed no significant difference between-group difference. <u>Pain control satisfaction</u> at 12 and 24 h was significantly higher in the gabapentin vs placebo groups (2 resp. 3 studies). <u>Maternal side effects</u> no significant differences (nausea, vomiting, pruritus, or shivering) were reported in any study regarding hypotension, and shivering.</p> <p>Author's Conclusion: In summary, prophylactic gabapentin 300 mg oral gabapentin prior to cesarean delivery improved postoperative pain control in healthy patients undergoing spinal anesthesia with intrathecal opioids as well as receiving standing NSAIDs and acetaminophen postpartum.</p>
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<p><b>Methodical Notes</b></p>
<p><b>Funding Sources:</b> None</p> <p><b>COI:</b> None</p> <p><b>Study Quality:</b> All the included studies had “low risk” of bias in “random sequence generation.” All the trials were placebo-controlled and participants nor the investigators were aware of the treatment assignments.</p> <p><b>Heterogeneity:</b> Statistical heterogeneity within the trials ranged from low to moderate with no inconsistency (I<sup>2</sup> = 0%) for secondary outcomes and I<sup>2</sup> = 89% for the primary outcome.</p> <p><b>Publication Bias:</b> Assessed statistically using Begg’s and Egger’s test, showed no significant bias (P = 0.57 and P = 0.52, respectively).</p> <p><b>Notes:</b> Oxford Level of Evidence: EL 1 (systematic review of randomized trials)</p> <p><b>Limitations:</b></p> <ul style="list-style-type: none"> <li>- only patients included receiving regional anesthesia with intrathecal opioids</li> <li>- only four of the included studies assessed the primary outcome (VAS pain score); the authors stated in the discussion, that the use of gabapentin showed a decrease in postoperative pain score and narcotic usage. The other two studies showed no difference.</li> <li>- small number of patients in the included studies (45-200 patients).</li> </ul>

Frauenknecht, J. et al. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. *BMJ* 2019; **374**: 651-662. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p><b>Study type:</b> Systematic review and meta-analysis (23 studies)</p> <p>This meta-analysis investigated whether opioid-inclusive, compared with opioid-free anaesthesia, would reduce postoperative pain, without increasing the rate of postoperative nausea and vomiting.</p> <p><b>Databases:</b> The electronic databases Medline and PubMed.</p> <p><b>Search period:</b> Inception - 06 / 2018.</p> <p><b>Inclusion Criteria:</b> The meta-analysis addresses men and women undergoing any surgical operation. Only trials investigating pain outcomes, and comparing any type of intra-operative opioid administration with placebo injection or absence of opioids, were included in the present meta-analysis. In publications where different doses were investigated within the intra-operative opioid regimen, we selected data from the group with the highest dose for analysis. The outcomes extracted from the retrieved articles were derived following our routine approach, described within our previous metaanalyses on acute postoperative pain and postoperative nausea and vomiting. The primary outcome was pain score at rest at two postoperative hours. Secondary outcomes related to acute pain included: pain score at rest at 12 and 24 postoperative hours; intravenous (i.v.) morphine consumption equivalents at 2 h, 12 h and 24 h postoperatively; and wound mechanical hyperalgesia threshold. We also aimed to capture the rates of postoperative nausea and vomiting within the first 24 h postoperatively; and hospital resource-related outcomes including length of stay in the recovery area and total hospital length of stay. Extracted trial characteristics included: the type of surgery; intra-operative opioid regimen; medication used for anaesthetic maintenance; and type of postoperative analgesia.</p> <p><b>Exclusion Criteria:</b> not described.</p>	<p><b>Population:</b> Men and women undergoing any surgical operation.</p> <p><b>Intervention:</b> Intra-operative opioid administration</p> <p><b>Comparison:</b> Placebo injection or absence of opioids</p>	<p><b>Primary:</b> Pain score at rest at 12 and 24 hours; intravenous morphine equivalents at 2 postoperatively; mechanical hyperalgesia threshold.</p> <p><b>Results:</b> The meta-analysis summary results showed that due to length, results from 23 randomised controlled trials including 1304 patients were identified. Pain score at rest at two postoperative hours was significantly lower in the opioid-inclusive and placebo groups with a risk ratio (95%CI) of 0.2 (0.1-0.3), p = 0.38 and no evidence of heterogeneity. This was high-quality evidence. The rate of postoperative nausea and vomiting was significantly reduced in the</p>

group, with a risk ratio of 0.77 (0.61–0.90) and high-quality evidence for a similar level of the recovery of the difference (95% CI: -8.2 to 9.3), mirroring the 0.90

Author's Conclusion: In conclusion, the quality evidence for inclusive anaesthesia compared with general anaesthesia, does not show the level of postoperative consumption of analgesic associated with postoperative vomiting. We believe these results will help to individualise a strategy on a patient-by-patient basis. The limited benefit from an individualised methodological approach to define the most appropriate anaesthetic strategy for each patient may reduce system resource

### Methodical Notes

**Funding Sources:** This work was supported by departmental funding (Department of Anaesthesia, Lausanne University Hospital) and grants from the Swiss Academy for Anaesthesia Research (SACAR), Lausanne, Switzerland (50,000 CHF, no grant number attributed) and from the Swiss National Science Foundation to support his clinical research (grant number 32003B\_169974/1). EA has also received an honorarium from B. Braun Medical AG. No other conflicts of interest

**COI:** Funding see above. No other conflicts of interest.

**Study Quality:** The Cochrane Collaboration's Risk of Bias Tool for randomised controlled trials was employed to assess the risk of bias in this randomised trial. Two authors independently screened, reviewed and scored the items for each trial using this method and extracted data. Disagreements with scoring or extracted data were resolved through discussion with a third author. GRADE quality of evidence was evaluated for each endpoint and was considered to be high with the exception of Wound healing, which was considered to be very low.

**Heterogeneity:** The coefficient I<sup>2</sup> was calculated to evaluate heterogeneity, with pre-determined thresholds defined for low (25%), moderate (50%) and high (> 75%) levels [21]. In cases of moderate or high heterogeneity, a random effects model was applied; otherwise a fixed effects model was used. Sensitivity analysis was performed on the primary outcome after excluding trials with high or unclear risk of performance bias. High heterogeneity for the main outcome I<sup>2</sup> = 84%.

**Publication Bias:** The likelihood of publication bias for our primary outcome was assessed by drawing a funnel plot of the mean pain score at rest on postoperative day 1 (y-axis) as a function of the mean difference of pain score at rest on postoperative day 1 (x-axis) using Duval and Tweedie's trim and fill test. No publication bias was detected.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

High heterogeneity for the main outcome I<sup>2</sup> = 84%, likely caused by the inclusion of any surgery, limits implications of the article

Galvin, I. M. et al. Pharmacological interventions for the prevention of acute postoperative pain in adults following brain surgery. *Syst Rev.* 2019. . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Cochrane Review (43 studies)</p> <p>Databases: 1. Cochrane Central Register of Controlled Trials (CENTRAL; Issue 9 2017); 2. MEDLINE (Ovid SP, 1966 to 28 November 2018); 3. Embase (Ovid SP, 1988 to 28 November 2018);</p>	<p>Population: Adults undergoing either supratentorial or infratentorial craniotomy or craniectomy either as elective or emergency procedure.</p>	<p>Primary: Mean differences in validated measures of acute postoperative pain intensity measured at the following times:</p> <ol style="list-style-type: none"> <li>anytime in the first six hours postoperatively;</li> <li>12 hours postoperatively</li> <li>24 hours postoperatively;</li> <li>48 hours postoperatively</li> </ol> <p>Secondary: 1. Analgesic success as measured by achievement of 'no or mild pain' with 'no worse than mild pain' being defined as a score of ≤ 3 on a visual analogue scale or ≤ 3/10 on a numerical rating scale. 2. Mean difference in additional analgesia requirement at the same time point</p>

<p>4. CINAHL (Ovid SP,1982 to 28 November2018); 5. Web of Science (1990 to 28 November 2018).</p> <p>The WHOICTRP, conference abstracts and ClinicalTrials.gov were also searched.</p> <p>Search period: see Databases</p> <p>Inclusion Criteria: Blinded and non-blinded, controlled, randomized trials.</p> <p>Exclusion Criteria: Review articles, observational studies, case reports, case series, non-randomized studies and studies that had no control groups. Studies that investigated the use of agents with analgesic potential for non-analgesic purposes. Neurosurgical procedures that did not involve accessing the brain such as spinal operations. Interventions that were specifically given for the relief of established acute pain after brain surgery as opposed to those given before pain had become established.</p>	<p>Intervention: Any pharmacological drug or pharmacological technique evaluated against a control.</p> <ol style="list-style-type: none"> <li>1. NSAIDs (8 studies);</li> <li>2. dexmedetomidine (4 studies);</li> <li>3. gabapentin or pregabalin (2 + 1 studies);</li> <li>4. acetaminophen (studies);</li> <li>5. scalp infiltration (studies); and</li> <li>6. scalp blocks (studies)</li> </ol> <p>Comparison: Control.</p>	<p>3. Mean difference in validated measures of sedation at the same time po .... 7. Rate of adverse events in the perioperative period.</p> <p>Results: Dexmedetomidine: 2 studies, n= 128 participants (Intravenous dosages ranged from 0.5 to 0.8 mcg/kg/hr with one study including a bolus loading dose. The timing and duration of infusions varied from 10 to 20 minutes, one hour before surgery ended.</p> <p>Pain post-Op (0-12 hours): The pooled estimate of effect for the MD in pain intensity was -0.89 (95% CI -0.51, P &lt; 0.00001), during the first six hours postoperatively and -0.42 (95% CI -1.21 to -0.42, P = 0.0004 at 12 hours postoperatively). Moderate (0-6h) to 12h) quality of evidence (small number of studies and participants). The pooled estimate of effect for the MD in pain intensity at 24 hours (95% CI -0.32 to 0.16, P = 0.52), which was not statistically significant.</p> <p>Additional analgesia requirements: 2 studies, n= 128 participants The pooled estimate of effect for the MD in additional analgesia requirement was -21.36 (95% CI -34.63 to -8.1, P = 0.002).</p> <p>Adverse events: Nausea and vomiting: Three studies (n= 261) RR dexmed. vs control was 0.43 (95% CI 0.06 to 0.40). Hypotension: Three studies (n= 184) RR dexmed. vs. control was 0.50 (95% CI 0.05 to 0.56), with all the events occurring in only one study.</p> <p>Gabapentin and Pregabalin: (600 mg Gaba, 150 mg Pregaba) Pregabalin or gabapentin may reduce pain up to 6 hours (2 studies, 202 participants), MD -1.15,95% CI -1.66 to -0.6, low-quality evidence). Pregabalin was examined analgesic efficacy at 12 hours showing significant benefit. No analgesic efficacy was shown at later times (24 hours, MD -0.29, 95% CI -0.78 to 0.20, low-quality evidence). Additional analgesia requirements were not significantly less (95% CI -1.10 to 0.35, 3 studies, 234 participants, low-quality evidence). Nausea and vomiting was significantly reduced (RR 0.51, 95% CI 0.29 to 0.77, 2 studies, 273 participants, low quality evidence). Results for other outcomes were imprecise (additional analgesia requirements: MD -0.37, 95% CI -1.10 to 0.36, 2 studies, 234 participants, low-quality evidence).</p> <p>Author's Conclusion: There is high-quality evidence that NSAIDs reduce pain at 24 hours postoperatively. The evidence for reductions in pain intensity in dexmedetomidine, pregabalin or gabapentin, scalp blocks, and scalp infiltration is less certain and of generally low quality. There is low-quality evidence that pregabalin or gabapentin may reduce additional analgesics requirements. There is evidence that gabapentin or pregabalin may decrease nausea and vomiting, with the caveat that the total number of events for this comparison is low.</p>
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<p><b>Methodical Notes</b></p>
<p>Funding Sources: None.</p> <p>COI: Imelda M Galvin: none known Ron Levy: none known Andrew G Day: none known Ian Gilron: see publication.</p> <p>Study Quality: Risk of bias of the studies for Gabapentin and Dexmedetomidin was mainly low. For quality of Evidence see results.</p> <p>Heterogeneity: Dexmedetomidine vs. control for acute pain at 24h was low.</p> <p>Publication Bias:</p> <p>Notes: CEBM Level of evidence (Oxford): EL 1 (systematic review of randomized trials).</p> <p>Notes: - Most studies focused on NSAIDs, which are the wrong intervention for this PICO. - Only three resp. two studies analyzed Dex and Gaba, so the impact of the results for the PICO are unclear.</p>

<p>Gehling, M. et al. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. <i>Anaesthesia</i> 2018; 73: 1033-1041.</p>		
<p>Evidence level/Study Types</p>	<p>P - I - C</p>	<p>Outcomes/Results</p>
<p>Evidence level: 2</p>	<p>Population:</p>	<p>Primary: Frequency of nausea, vomiting, pruritus, urinary retention and respiratory.</p>

<p><b>Study type:</b> Systematic review and meta-analysis</p> <p>Intrathecal morphine is often used for postoperative analgesia after surgery. We performed a meta-analysis to obtain more detailed information on the frequency of side-effects in patients receiving intrathecal morphine in combination with spinal anaesthesia compared with placebo treated patients.</p> <p>Databases: Medline</p> <p>Search period: Inception - 2007.</p> <p><b>Inclusion Criteria:</b> Studies met inclusion criteria if they investigated intrathecal morphine for postoperative analgesia in a randomised, placebo-controlled trial. The restriction to placebo controlled studies was necessary in order to calculate the risk ratio. However, patients in the placebo groups often received systemic opioids for postoperative analgesia.</p> <p><b>Exclusion Criteria:</b> Not specified.</p>	<p><b>Patients</b> undergoing operations and anaesthesia (included were Caesarean sections, Orthopaedics, Transurethral prostatectomy, Total hip replacement, Haemorrhoids, Gynaecology etc.)</p> <p><b>Intervention:</b> Intrathecal morphine for postoperative analgesia</p> <p><b>Comparison:</b> Placebo, (but patients in the placebo groups often received systemic opioids for postoperative analgesia).</p>	<p><b>Secondary:</b> not specified.</p> <p><b>Results:</b> Results: only summary results displayed here due to length. We performed a meta-analysis to obtain more detailed information on the frequency of effects in patients receiving intrathecal morphine in combination with spinal anaesthesia compared with placebo treated patients. We clustered the analysis to patients receiving placebo, less than morphine 0.3 mg (M &lt; 0.3), or equal to or more than morphine 0.3 mg (M ≥ 0.3) and calculated the risk ratios of morphine vs placebo. Twenty-eight studies investigating 46 morphine groups vs placebo were included. A total of 790 patients receiving intrathecal morphine and 524 patients who received placebo were analysed. Compared with placebo the lower dose of morphine resulted in an increase of nausea (RR 1.4, 95% CI 1.1–1.7), vomiting (RR 3.1, 95% CI 1.5–6.4) and pruritus (RR 1.8, 95% CI 1.4–2.2). The higher dose of morphine resulted in an increased risk ratio for pruritus (RR 5.0, 95% CI 2.9–8.6), but not nausea (RR 1.2, 95% CI 0.9–1.6) or vomiting (RR 1.3, 95% CI 0.9–1.9). Overall, intrathecal morphine did not increase respiratory depression. However, the higher dose of intrathecal morphine was associated with more episodes of respiratory depression (7 / 80) compared with the lower dose (2 / 247). Intrathecal morphine is associated with a mild increase in side-effects. At a dose &lt; 0.3 mg we found there were no more episodes of respiratory depression than placebo patients who received systemic opioid analgesia.</p> <p><b>Author's Conclusion:</b> Overall, the moderate incidence of side-effects seems to be justified by the quality and duration of analgesia provided by low dose intrathecal morphine in combination with a spinal anaesthesia. We conclude that intrathecal morphine for postoperative analgesia requires measures for prophylaxis and therapy of side-effects and continuous observation of the respiratory function of patients. The same is true, however, for patients who receive opioids systemically. There are no data to support the need for extended monitoring of patients who receive low dose intrathecal morphine.</p>
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#### Methodical Notes

**Funding Sources:** Not declared.

**COI:** Not declared.

**Study Quality:** The quality of included reports was analysed according to recommendations described by McQuay and Moore [1]. The method score was calculated from documented randomisation, blinding and withdrawals. The greater the method score the better the quality of the trial. In a subgroup analysis we calculated the outcome parameters for each method score.

"Six studies had a method score of 5, six had a score of 4, 13 trials had a score of 3 and three trials had a score of 2."

**Heterogeneity:** We used the fixed effects model and analysed heterogeneity with Cochrane's Q and I<sup>2</sup> tests as a measure of increased heterogeneity indicates the risk of misinterpretation due to differences in study design. The forest plot gives an idea of the effect size and 95% confidence interval (CI) for each study. Cochrane's Q is a statistical measure of heterogeneity due to squared differences between individual study effects and the pooled effect across studies. As a more intuitive parameter of relation between the difference of Q minus the degree of freedom and Q. It gives a result expressed in percentage of variation chance.

"We found no significant heterogeneity within the analysed subgroups for nausea, vomiting, pruritus, urinary retention or respiratory depression."

**Publication Bias:** Publication bias not investigated.

#### Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis

Downgrade to evidence level 2

Using a single database is not considered a comprehensive literature search. No declarations of interest or funding. Publication bias not investigated. Significant heterogeneity within the analysed subgroups for nausea, vomiting, pruritus, urinary retention or respiratory depression.

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (23 studies) The effect preoperative pregabalin on postoperative nausea and vomiting (PONV). Databases: MEDLINE, EMBASE, and CINAHL.</p> <p>Search period: Inception - 03 / 2015.</p> <p>Inclusion Criteria: (1) population: studies involving adult (age &gt;18 years) human patients undergoing surgery under general anesthesia; (2) intervention: preoperative oral pregabalin administered ≥30 minutes before surgical incision; (3) predefined outcomes: incidence of postoperative nausea, vomiting, PONV, and rescue antiemetic administration within 24 hours of surgery; and (4) design: randomized controlled trials published in English, full-text versions. No minimal sample size or dosing regimen was required for inclusion.</p> <p>Exclusion Criteria: -</p>	<p>Population: Adult (age &gt;18 years) human patients undergoing surgery under general anesthesia.</p> <p>Intervention: Preoperative oral pregabalin administered ≥30 minutes before surgical incision</p> <p>Comparison: control unclear definition. Table 1 states "All included trials utilized placebo for their control group."</p>	<p>Primary: incidence of postoperative nausea, vomiting, POI rescue antiemetic administration within 24 hours of surgery</p> <p>Secondary: -</p> <p>Results: Only summary results presented to to length. Among all included trials (23 trials; n = 1693), preop pregabalin was associated with a significant reduction in POI ratio [RR] = 0.53; 95% confidence interval [CI], 0.39–0.70.0001), nausea (RR = 0.62; 95% CI, 0.46–0.83; P = 0.0001), vomiting (RR = 0.68; 95% CI, 0.52–0.88; P = 0.003) at 24 hours. Subgroup analysis designed to account for major confounders, including the exclusion trials with repeat thiopental induction, nitrous oxide maintenance, and propl antiemetics and including high-risk surgery, resulted in significantly increased rates of postoperative visual distu (RR = 3.11; 95% CI, 1.34–7.21; P = 0.008) compared with a con</p> <p>Author's Conclusion: Preoperative pregabalin is associat significant reduction of PONV and should not only be consid part of a multimodal approach to postoperative analgesia b for prevention of PONV.</p>

**Methodical Notes**

Funding Sources: None.

COI: The authors declare no conflicts of interest.

Study Quality: A Jadad score was calculated by two investigators for each individual trial, which is based on whether t appropriate randomization, (b) appropriate double blinding, and (c) complete account for participant withdrawals or dropouts. E and their sum (5 representing a perfect score) is the Jadad score.

Heterogeneity: Heterogeneity was measured and expressed as I<sup>2</sup>, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I<sup>2</sup> was calculated from basic results obtained from a typical metaanalysis as I<sup>2</sup> = 100% × (Q - heterogeneity statistic).

Publication Bias: Funnel plots of the incidence of various end points were used to assess for publication bias when >10 compar endpoint. Publication bias was assessed by inspection of the funnel plot and by formal testing "funnel plot" asymmetry using th

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis  
Unclear definition of comparator in the inclusion or in general.

**Hamilton, T. W. et al. A Meta-Analysis on the Use of Gabapentinoids for the Treatment of Acute Postoperative Pain Followed by Total Knee Arthroplasty. J Bone Joint Surg Am. 98. 1340-50. 2016**

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR and META (of 12 RCTs) Databases: MEDLINE [Ovid], Embase [Ovid], and Web of Science [ISIWeb of Knowledge], reference lists and registers of controlled clinical trials</p> <p>Search period:</p>	<p>Intervention: Oral gabapentinoid class of drugs gabapentin [Neurontin; Pfizer] or pregabalin [Lyrica; Pfizer]</p> <p>Comparison:</p>	<p>Primary: Pain intensity with activity at 48 hours. In cases in which pain with activity not reported, pain at rest was used if available.</p> <p>Secondary: Pain scores at 12, 24, and 72 hours; cumulative opioid consumption (0 to 48 hours); knee flexion at 48 hours; incidence of chronic pain; and adverse events (sedation, c and pruritus; 0 to 72 hours). For opioid consumption, the reported consumption was converted to the oral mo dose.</p> <p>Results:</p> <p>12 RCTs compared the use of gabapentin (5 studies) or pregabalin (7 studies) with t no treatment, in patients undergoing elective primary total knee arthroplasty. No c</p>

<p><b>MEDLINE, Embase, and Web of Science</b> were searched from their inception until September 8, 2015.</p> <p><b>Inclusion Criteria:</b> Patients who were <math>\geq 18</math> years of age and were undergoing elective primary total knee arthroplasty. There was no restriction with respect to studies that investigated single or multiple dosing schedules and preoperative or both preoperative and postoperative dosing, or with respect to the type of anesthesia.</p> <p><b>Exclusion Criteria:</b></p>	<p>Placebo or no treatment</p>	<p>score at 12, 24, 48, or 72 hours following the surgical procedure was seen between placebo. Although pregabalin was associated with reduced pain scores at 24 and 48 hours, this corresponded to a reduction of 0.5 point (95% confidence interval, 0 to 1.0 point) at 24 hours and 0.6 point (95% confidence interval, 0 to 0.6 point) at 48 hours on an 11-point numeric rating scale. Although pregabalin was associated with a reduction in cumulative opioid consumption at 48 hours (mean difference, 223.2 mg [95% confidence interval, 240.9 to 25.4 mg]). There was no difference in cumulative opioid consumption at 24 hours (p = 0.63) or in the incidence of chronic pain at 3 months (p = 0.31) or 6 months (p = 0.31) associated with the use of gabapentinoids. Although gabapentinoids were associated with a reduction in the incidence of nausea (risk ratio, 0.7 [95% confidence interval, 0.6 to 0.8]; p = 0.02), pregabalin was also associated with a significant, clinically relevant increase in the incidence of nausea (risk ratio, 1.4 [95% confidence interval, 1.1 to 1.9]; p = 0.02).</p> <p><b>Author's Conclusion:</b> In summary, based on our meta-analysis, we found no evidence to support the routine use of gabapentinoids in the management of acute postoperative pain following total knee arthroplasty. Although some analgesic efficacy and opioid-sparing effects were seen with the use of pregabalin, these were unlikely to be of clinical importance. Additionally, no benefit was seen in improving short-term function or reducing the long-term incidence of chronic pain with the use of pregabalin, although an anti-emetic effect was observed, a significant increase in the risk of serious adverse events with the use of pregabalin was detected. Further high-quality randomized controlled trials in those investigating patients at high risk of chronic pain, may yield positive results for the use of gabapentinoids; however, the current evidence does not support the routine use of gabapentinoids or an enhanced recovery program for total knee arthroplasty.</p>
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<p><b>Methodical Notes</b></p>	
<p><b>Funding Sources:</b> None reported</p>	
<p><b>COI:</b> (T.W.H.) received a grant from the National Institute for Health Research (NIHR) Biomedical Research Unit into Musculoskeletal Health at the Oxford Orthopaedic Centre and the University of Oxford; funds were used to pay for his time to complete this work.</p>	
<p><b>Study Quality:</b> Studies included parallel-group, blinded, randomized controlled trials. The results from the study by Brackel et al. were presented in a manner that prevented their inclusion in the quantitative analysis. The study by Brackel et al., was treated as two separate comparisons within the same study because of the combinations of drugs and placebo used. Lack of blinding, lack of placebos or the method of random sequence generation, presenting a high risk of performance bias and an unclear risk of bias. Singla et al. did not report information regarding allocation concealment, blinding of participants and personnel, and outcome reporting bias, presenting a high risk of bias. Additionally, only 69% of participants in that study completed treatment, giving a high risk of attrition bias. The manufacturer of the trial drug, presenting an unclear risk of other bias. A sensitivity analysis was performed on the basis of the results of the studies at high risk of bias did not change the interpretation of the results.</p>	
<p><b>Heterogeneity:</b> Heterogeneity of data was assessed using the I<sup>2</sup> statistic. In cases in which substantial heterogeneity of a data set was observed, a meta-analysis was not performed.</p>	
<p>Pain intensity at 48 hours (n=8): high heterogeneity seen (I<sup>2</sup> = 73%). Pain intensity at 12 hours (n=4): (1 on gabapentin and 3 on pregabalin) high heterogeneity (I<sup>2</sup> = 88%)</p>	
<p><b>Publication Bias:</b> None reported</p>	
<p><b>Notes:</b> Oxford level of evidence: 1 Systematic review and meta-analysis Für Pregabalin siehe Doppelpublikation (Han 2017) with different outcome/interpretation (relevance). <b>Limitations:</b> -insufficient studies to permit evaluation of different dose regimens, timings, and frequency of gabapentinoids -different anesthetic and perioperative analgesic regimes as well as patient differences, significant heterogeneity was observed and</p>	

<p>Han, C. et al. Is pregabalin effective and safe in total knee arthroplasty? A PRISMA-compliant meta-analysis of randomized controlled trials. <i>Journal of Orthopaedics and Traumatology</i> (Baltimore). 96. e6947. 2017</p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	
<p>Evidence level: 1</p> <p>Study type: SR and META (of 7 RCTs)</p> <p>Databases: MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials</p> <p>Search period: MEDLINE (1966 to June 2016), EMBASE (1966 to June</p>	<p>Population: Patients with unilateral TKA only.</p> <p>Intervention: Pregabalin</p> <p>Comparison: Placebo</p>	<p><b>Primary:</b> Cumulative consumption of morphine, visual analogue scale (VAS) score, range, and adverse effects.</p> <p><b>Secondary:</b> see primary outcome</p> <p><b>Results:</b> In all pooled literatures, “Singla 2015 (150mg)” and “Singla 2015 (300mg)” were the only studies that divided this trial into 2 different dose comparisons (150mg pregabalin vs. placebo and 300mg pregabalin vs. placebo). “YaDeau 2015 (50 mg),” “YaDeau 2015 (100 mg),” and “YaDeau 2015 (150mg)” were also belonged to 1 study, we divided this study into 3 different dose comparisons (50mg pregabalin vs. placebo; 100mg pregabalin vs. placebo; and 150mg pregabalin vs. placebo).</p>	



2016), and Cochrane Central Register of Controlled Trials (search period is not listed).

**Inclusion Criteria:** The search was limited to RCTs in humans up to June 2016. : RCTs with placebo, report in English. Patients with unilateral TKA only.

**Exclusion Criteria:** Patients were excluded from this work if they had bone neoplasms, serious osteoporosis, infection, metal sensitivity, or mental diseases.

Postoperative narcotic requirements at 24 and 48h (n=7): The pooled results from the meta-analysis showed a positive, the effect of pregabalin in all trials, significantly reducing postoperative narcotic consumption at 24h (MD=-3.27, 95% CI: -6.05 to -0.49, P<.00 and ci: to p=".002)." However, significant heterogeneity was found in  $df=6$ ,  $I^2=82\%$ ,

Passive knee flexion range at 48h (n=4): Significant heterogeneity was found ( $I^2=97\%$ , P<.00) therefore a random model was performed. compared with placebo, pregabalin significantly increase postoperative passive knee flexion range at ci:  $p=.02$ .

Postoperative VAS at 24 (n=7)and 48h (n=3): Significant heterogeneity was found ( $I^2=74\%$ , P<.00  $x^2=13.79$ ,  $df=2$ ,  $I^2=76\%$ ,) therefore a random model was performed. The meta-analysis showed that no significant difference found in pregabalin groups compared with placebo preoperatively and postoperatively ci: to  $smd=-0.50$ ,

Adverse effects: rate of nausea(n=8), which was the most common adverse effect after TKA. Significant heterogeneity was not found in the included studies; therefore, a fixed model was used ( $x^2=9.52$ ,  $df=7$ ,  $I^2=27\%$ , P=.22). Compared with placebo, pregabalin could significantly decrease the incidence rate of nausea postoperatively (relative rate 0.71, 95% CI: 0.59–0.86, P=.001). No significant heterogeneity was found therefore a fixed model used  $df=4$ ,  $I^2=0\%$ , compared with the placebo group incidence rate of less in pregabalin groups ci:>

Incidence rate of vomiting (n=4): No significant heterogeneity was found, a fixed model was applied ( $x^2=2.33$ ,  $df=3$ ,  $I^2=0\%$ , P=.51). Compared with the control group, pregabalin could significantly decrease the incidence rate of vomiting (relative rate 0.54, 95% CI: 0.37–0.78, P=.001). Incidence rate of constipation (n=3): Significant heterogeneity was not shown between pooling results, a fixed model was applied ( $x^2=3.54$ ,  $df=2$ ,  $I^2=43\%$ , P=.17). Compared with the control group, pregabalin could significantly decrease the incidence rate of constipation as well (relative rate 0.45–0.89, P=.009).

Incidence rate of somnolence (n=5): Significant heterogeneity was not found; therefore, a fixed model was applied ( $x^2=1.88$ ,  $df=4$ ,  $I^2=0\%$ , P=.76). Compared with the control group, pregabalin was more found in the pregabalin groups (relative rate 1.29, 95% CI: 1.00–1.68, P=.05).

Incidence rate of dizziness (n=5): Significant heterogeneity was not found, a fixed model was applied ( $x^2=1.95$ ,  $df=4$ ,  $I^2=0\%$ , P=.74). Compared with the control group, the incidence rate of dizziness was more in the pregabalin group (relative rate 1.46, 95% CI: 1.04–2.06, P=.03).

Incidence rate of confusion (n=5): Significant heterogeneity was not found; therefore, a fixed model was applied ( $x^2=0.99$ ,  $df=4$ ,  $I^2=0\%$ , P=.91). Compared with the control group, confusion was more found in the pregabalin groups (relative rate 2.44, 95% CI: 1.36–4.38, P=.003).

Incidence rates of headache, peripheral edema, and urinary retention (n=5): Significant heterogeneity was not found in those studies, a fixed model was used ( $x^2=3.73$ ,  $df=2$ ,  $I^2=0\%$ , P=.16; Fig. 13;  $x^2=0.29$ ,  $df=2$ ,  $I^2=0\%$ , P=.86; Fig. 14;  $x^2=0.27$ ,  $df=2$ ,  $I^2=0\%$ , P=.87). Compared with the control group, no significant difference was found in pregabalin groups (relative rate 0.75, 95% CI: 0.42–1.36, P=.35; relative rate 0.84, 95% CI: 0.37–1.46, P=.38; relative rate 0.75, 95% CI: 0.42–1.36, P=.35; relative rate 0.84, 95% CI: 0.37–1.46, P=.38).

**Author's Conclusion:** This meta-analysis of RCTs studies reveals that pregabalin was effective in the reduction of postoperative narcotic requirements, passive knee flexion range, and incidence of some adverse effect after TKA.

#### Methodical Notes

Funding Sources: None

COI: None

Study Quality: The risk of bias was assessed according the Cochrane Collaboration's tool, and the quality of the RCTs was evaluated. No risk of bias was found in all included studies.

**Heterogeneity:**

By the usage of chisquared test, heterogeneity was evaluated by the value of P and I2. P>.10 and I2<50% were defined as hav (see results). Then, a fixed-effects model was applied for data analysis. A random-effects model was used when the significant h

**Publication Bias:** Not assessed

**Notes:**

CEBM Level of Evidence (Oxford): EL 1 (Systematic review of randomized trials. Achtung Doppelpublikation (Li F et al. 2017). Hie

**Notes:**

- 7 trials were included but some trails tested different doses of pregabalin. The authors regarded these different doses as sep YaDeau 2015 analysed 50 mg, 100mg and 150 mg pregabalin each vs. placebo =>tree different trials). Thus in total a maximum c each outcome.

- high heterogeneity due to various study designs, administration time and doses of pregabalin.

- small study groups

**Han, C. et al. The Efficacy of Preoperative Gabapentin in Spinal Surgery: A Meta-Analysis of Randomized Controlled T 661. 2017**

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR and META (of 10 RCTs)</p> <p>Databases: MEDLINE, EMBASE, ClinicalTrials.gov, and Web of Science databases were systematically searched</p> <p>Search period: Not stated.</p> <p>Inclusion Criteria: Only RCTs for spinal surgery in humans were included.</p> <p>Types of studies: published in the English language</p> <p>Exclusion Criteria:</p>	<p>Population: see inclusion criteria</p> <p>Intervention: Gabapentin</p> <p>Comparison: Placebo</p>	<p><b>Primary:</b> The cumulative consumption of morphine at 24 hours, the pain assessment score, or the incidence of adverse effects.</p> <p><b>Secondary:</b> see primary outcome.</p> <p><b>Results:</b> 10 RCTs to eventually fulfill the selection criteria. A total of 827 patients were incl research time interval was between 2004 and 2016.</p> <p><b>Cumulative Consumption of Morphine at 24 Hours:</b> 300 mg of Gabapentin (n=3): The pooled meta-analysis showed a positive effect of gabapentin in trials (MD = -1.74, 95% CI: -2.5 0.00). No significant heterogeneity was found in the included studies (<math>\chi^2 = 3.15</math>, df = 2, I2 = 3 600 mg of Gabapentin (n=3): Compared with the placebo, gabapentin could significantly postoperative consumption of morphine (MD = -5.36, 95% CI: -6.27 to -4.45, P &lt; 0.00). heterogeneity was found in all of the included studies (<math>\chi^2 = 1.41</math>, df = 2, I2 = 0%, P = 0.4 Gabapentin (n=4): Compared with the placebo, gabapentin showed a positive effectin the postoperative consumption of morphine (MD = -11.41, 95% CI: -19.75 to -3.08, P &lt; 0. significant heterogeneity was found in the included studies (<math>\chi^2 = 195.05</math>, df = 3, I2 = 98%, P &lt; of Gabapentin (n=4): The pooled results from the meta-analysis showed a positive effect of trials (MD = -17.84, 95% CI: -28.20 to -7.47, P &lt; 0.00). However, significant heterogeneity was the included studies (<math>\chi^2 = 71.03</math>, df = 3, I2 = 96%, P &lt; 0.00).</p> <p><b>Postoperative VAS Score at 2 Hours (n=5):</b> Significant heterogeneity was found (<math>\chi^2 = 44.98</math>, d P &lt; 0.00); therefore, a random-effects model was performed. Compared with the placebo, gab significantly reduce the postoperative VAS score at 2 hours (MD = -15.16, 95% CI: -23.75 to - Postoperative VAS Score at 4 Hours (n=4): Significant heterogeneity was found (<math>\chi^2 = 123. 94%</math>, P &lt; 0.00); then, the random-effects model was performed. The result revealed a pos gabapentin on the reduction of postoperative VAS scores at 4 hours (MD = -15.96, 95% CI: -2. 0.0002). Postoperative VAS Score at 6 Hours (n=11): Significant heterogeneity exists (<math>\chi^2 = 1 I2 = 93%</math>, P &lt; 0.00); therefore, a random-effects model was performed. Compared with gabapentin could reduce the VAS score at 6 hours significantly (MD = -14.32, 95% CI: -20.7 0.00). Postoperative VAS Score at 12 Hours (n=6): Significant heterogeneity was found random-effects model was used (<math>\chi^2 = 87.01</math>, df = 12, I2 = 0%, P &lt; 0.00). The overall pooled re meta-analysis showed that gabapentin is quite effective in reducing the VAS score at 12 hour 95% CI: -15.76 to -7.53, P &lt; 0.00). Postoperative VAS Score at 24 Hours (n=11): Significant exists (<math>\chi^2 = 57.47</math>, df = 12, I2 = 79%, P &lt; 0.00); then, a random-effects model was performed. C the placebo, gabapentin could reduce the postoperative VAS score at 24 hours significantl 95% CI: -11.76 to -5.80, P &lt; 0.00; Fig. 8).</p> <p><b>Adverse Effects:</b> The incidence rate of vomiting, pruritus, and urinary retention was significat gabapentin groups (RR = 0.53, 95% CI 0.32–0.86, P &lt; 0.05; RR = 0.38, 95% CI 0.22–0.66, P &lt; 0 95% CI 0.34–0.98, P &lt; 0.05, respectively). For more details see publication.</p>
<p><b>Author's Conclusion:</b> This meta-analysis of RCTs reveals that pre-emptive utilization of gab</p>		

significantly reduce postoperative VAS scores, postoperative morphine consumption at 24 h, and incidence rates of some adverse effects in spinal surgery.

## Methodical Notes

**Funding Sources:** No external funding.

**COI:** None

**Study Quality:** The risk of bias was assessed according to the Cochrane Collaboration's tool, and the quality of the RCTs was evaluated. No risk of bias was found in all of the included studies.

**Heterogeneity:** By the usage of chi-square tests, heterogeneity was evaluated by the value of I<sup>2</sup> and P; I<sup>2</sup> < 50% and P = 0.1 was considered as no substantial heterogeneity. Statistical heterogeneity was found in the meta-analysis. A subgroup analysis was performed to evaluate the results. A subgroup analysis was carried out to find the source of heterogeneity. Factors such as dosage discrepancy, and age differences caused the heterogeneity.

**Publication Bias:** A funnel plot shows a symmetrical shape.

### Notes:

**CEBM Level of Evidence (Oxford):** EL 1 (Systematic review of randomized trials)

Only 10 RCTs met our inclusion criteria, so the sample size was still relatively small (19-38 patients). In 2 trials, gabapentin was given postoperatively, whereas in the other 8 trials, gabapentin was given preoperatively only. In 3 trials, multiple dosages were used as separate trials in their analysis for VAS scores and adverse events (e.g. Khan 2011 analysed 600 mg, 900 mg and placebo => three different trials).

Hu, J. et al. Effects of a single dose of preoperative pregabalin and gabapentin for acute postoperative pain: a network meta-analysis of randomized controlled trials. *J Pain Res.* **11.** 2633-2643. 2018

## Evidence level/Study Types

## P - I - C

## Outcomes/Results

**Evidence level:** 1

**Study type:** Network META analysis (79 RCTs)

**Databases:** PubMed, Embase, and the Cochrane Library.

**Search period:** last update of search 3.12.2017

**Inclusion Criteria:** Randomized clinical trials were included if they satisfied the following selection criteria: 1) premedication with single dose of PGB or GBP; 2) acute postoperative pain; and 3) operation under intravertebral anesthesia or general anesthesia.

**Exclusion Criteria:** 1) multiple-dose oral administration of PGB and GBP (long-term preoperative administration or postoperative administration); 2) chronic postoperative pain; 3) operation under local anesthesia; 4) unable to extract any data; and 5) not published in English or Chinese.

**Population:** In total 6,201 patients were included in the analysis.

These studies were performed from 2002 to 2017 in 23 countries. Patients included in the studies underwent various types of surgeries: obstetrics and gynecology surgery (22.8%), spinal surgery (10.1%), orthopedic joint surgery (17.7%), urology surgery (7.6%), visceral surgery (16.4%), cardiac surgery (3.8%), and others (20.3%).

**Intervention:** Premedication with single dose of PGB or GBP: placebo (PBO), PGB 75 mg, PGB 150 mg, PGB 300 mg, GBP 300 mg, GBP 600 mg, GBP 900 mg, and GBP 1,200 mg.

**Comparison:** Placebo

**Primary: Analgesic effect):** 1) opioid consumption at rest (visual analog scale or numerical rating scale), and 3) pain score at movement recorded within 24 hours after surgery.)

**Secondary: Adverse events):** 1) PONV, 2) nausea and vomiting within 24 hours after surgery; 3) vomiting; and 4) dizziness.

**Results:** 62 studies (78.5%) used general anesthesia, the others (21.5%) used spinal anesthesia. Administration time varied between these groups: ≤1 hour before surgery, (41.8%) >1 hour before surgery, (17.7%) ≤1 hour before anesthesia, and before anesthesia.

### Analgesic effects:

**Opioid consumption:** 52 studies, n= 3,827 patients. All interventions consumed less opioid than control. Administration of increasing dose of PGB significantly decreased the consumption of opioids. PGB 150 mg vs PBO: SMD -1.66, 95% CI -1.86 to -1.46; PGB 300 mg vs PBO: SMD -1.86, 95% CI -2.06 to -1.66; GBP 300 mg vs PBO: SMD -0.98, 95% CI -1.18 to -0.78; GBP 600 mg vs PBO: SMD -1.14, 95% CI -1.34 to -0.94; GBP 900 mg vs PBO: SMD -1.64, 95% CI -1.84 to -1.44; GBP 1,200 mg vs PBO: SMD -1.86, 95% CI -2.06 to -1.66. No significant differences were found between interventions and control groups.

**Pain score at rest:** 48 studies, n= 3,664 patients. Patients with PGB (150/300 mg) and GBP (300/600 mg) exhibited significantly less pain compared to PBO.

PGB 150 mg vs PBO: SMD -0.96, 95% CI -1.16 to -0.76; PGB 300 mg vs PBO: SMD -0.50, 95% CI -0.70 to -0.30; GBP 900 mg vs PBO: SMD -1.11, 95% CI -1.31 to -0.91; GBP 1,200 mg vs PBO: SMD -0.89, 95% CI -1.09 to -0.69. No significant differences were found between interventions and control groups.

**Pain score at movement:** 15 studies, n= 1,500 patients. No significant differences were found between interventions and control groups.

**Secondary outcomes:**

PGB 300 mg reduced the incidence of PONV vs PBO: OR 0.18, 95% CI 0.09, 0.37) and mg vs PBO: OR 0.50, 95% CI 0.35, 0.72) control groups.

Patients with GBP 1,200 mg showed high PONV (GBP 1,200 mg vs PBO: OR 5.21, 95% CI 1.10, 24.1). However, incidence of dizziness increased when 1,200 mg or PGB 300 mg was used (PGB 150 mg vs PBO: OR 1.94, 95% CI 1.10, 3.42; PGB 300 mg vs PBO: OR 1.46, 95% CI 1.46, 4.23). No significant difference was found between the interventions and control groups for the incidence of vomiting.

**Author's Conclusion:** The results of this study demonstrated that a dose-response relationship was detected in opioid consumption and postoperative nausea and vomiting after a single-dose preoperative administration of gabapentin. Making a reasonable choice of drugs and dosages to prevent the occurrence of adverse effects in clinical trials are required to determine the optimal analgesic effect between single-dose oral administration and intravenous administration. Furthermore, the optimal dosages, medications and timing of administration for analgesia still require further study, which will help to standardize and rationalize analgesia.

**Methodical Notes**

**Funding Sources:** The project was supported by the Natural Science Foundation of Zhejiang Province (LY16H290003 to Juan Zhang).

**COI:** None.

**Study Quality:** The Cochrane Collaboration's Risk of Bias Tool was used for randomized controlled trials to estimate the quality assessment of the included study. The most common high risk of bias was selective reporting, which resulted from the consideration of incomplete outcome data.

**Heterogeneity:** Sensitivity analysis were performed, overall effect was not markedly affected. Heterogeneity variance was 1.19.

**Publication Bias:** Risk of publication bias was indicated by funnel plots. No risk of publication bias was found for any outcomes.

**Notes:**  
CEBM Level of evidence (Oxford). EL 1 (Systematic review of randomized trials).

**Notes:**  
- the use of pregabalin (PGB) or gabapentin (GBA) for the management of postoperative pain is off-label.  
  
- the majority of the here included studies overlap with the review of Fabritius et al. 2016. Whereas the interpretation of results and relevance of both studies is quite different evaluated between the two groups of authors.

**Jessen Lundorf, L. et al. Perioperative dexmedetomidine for acute pain after abdominal surgery in adults. Cochrane Database of Systematic Reviews 2016**

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 5); MEDLINE, Ovid SP (1956 to May 2014); EMBASE, Ovid SP (1982 to May 2014); Institute for Scientific Information (ISI) Web of Science (1950 to May 2014) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO host (1980 to May 2014). We searched the Science</p>	<p><b>Population:</b> Adults receiving dexmedetomidine for acute pain after abdominal surgery including both open and laparoscopic procedures, irrespective of language and publication status.</p> <p><b>Intervention:</b> We compared perioperative (preoperative, intraoperative or postoperative) administration of dexmedetomidine with other treatments or placebo (with 'rescue' medication). We included all modes of administration and all variations of dosage, frequency and duration. We included interventions combining dexmedetomidine with another treatment if that same treatment, without dexmedetomidine, was given to the control group. We also included interventions combining dexmedetomidine with another treatment if the design of the trial was factorial, and if we did not suspect any</p>	<p><b>Primary:</b> - The opioid-sparing effect of dexmedetomidine by amount of 'rescue' opioid, administered via any route, 12 and 24 hours after end of surgery. - The analgesic efficacy of dexmedetomidine - measured on movement, as defined by study authors, by visual analogue scale (VAS) 0 to 100 mm, where 0 mm corresponds to no pain and 100 mm corresponds to worst imaginable pain. Use of a VAS was converted to VAS 0 to 100 mm.</p> <p><b>Secondary:</b> - Time to first request of 'rescue' analgesia - Proportion of participants needing 'rescue' analgesia - Postoperative sedation - assessed by clinical measurement at 12 and 24 hours after end of surgery - Proportion of participants with PONV until 24 hours after end of surgery - Time to first passage of flatus after end of surgery - Time to first passage of stool after end of surgery - Time to first out-of-bed mobilization after end of surgery - Proportion of participants with delay to first out-of-bed mobilization</p>

Citation Index, ClinicalTrials.gov and Current Controlled Trials in August 2014 to identify additional published, unpublished and ongoing studies.

Search period: See databases.

Inclusion Criteria: We included adult participants undergoing all types of abdominal surgery, including both open and laparoscopic procedures, general and regional forms of anaesthesia. We defined abdominal surgery as surgery to intra-abdominal organs.

Exclusion Criteria: Cross-over trials, quasi-randomized trials and all nonrandomized trials; gynaecological, urological, vascular and superficial surgery (such as hernia repair);

interaction between treatments.

Comparison: see intervention.

- Post-interventional complications or adverse effects: hypotension, bradycardia, delirium and respiratory as a proportion of participants.

Results: The total number of participants was 422, and ranged from 20 to 80 participants.

For the comparison dexmedetomidine versus placebo (402 participants), most studies found a reduction in consumption in the first 24 hours after surgery, with general no clinically important differences in postoperative pain (visual analogue scale (VAS) 0 to 100 mm, where 0 = no pain, 100 = worst imaginable pain) in the first 24 hours after surgery for one study (80 participants) with a reduction in pain 24 hours after surgery in favour of dexmedetomidine (mean difference of -30.00 mm (95% confidence interval (CI) -45.00 to -15.00)).

Secondary outcome: Regarding our secondary aims, evidence was too sparse to allow robust conclusions, or the estimates too imprecise due to methodological quality. Regarding adverse effects, (one study, 80 participants) suggest that the participants with hypotension requiring intervention were higher in the high-dose dexmedetomidine group with risk ratio of 2.50 (95% CI 0.94 to 6.66), but dexmedetomidine led to no differences compared with placebo.

Author's Conclusion: Dexmedetomidine, when used perioperatively for acute pain after abdominal surgery, seemed to have some opioid sparing effect together with placebo. However the quality of the evidence was low due to result of imprecision, methodological limitations and heterogeneity among the seven included studies. The clinical importance for patients is uncertain, in as much as the benefits of dexmedetomidine on patient-important outcomes such as gastrointestinal function, mobilization and adverse effects could not be satisfactorily determined. All included studies were small, and publication bias could not be ruled out. The evidence was limited to middle-aged participants who were free of co-morbidity and were undergoing elective abdominal surgery. A potential bias was a considerable quantity of unobtainable data from studies with mixed surgery. To investigate patient-important outcomes, larger studies with longer periods of follow-up are needed.

#### Methodical Notes

Funding Sources: Herlev University Hospital, Denmark (Internal sources of support).

COI: None known.

Study Quality: We performed the assessment of risk of bias as recommended in the Cochrane Handbook for Systematic Reviews. The quality of the included studies had an unclear risk of bias.

We used the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system in our review. The body of evidence associated with specific outcomes.

As the result of substantial heterogeneity, pooling of data in statistical meta-analyses was not appropriate. The quality of evidence was low because of imprecision of results and risk of bias.

Heterogeneity: We considered heterogeneity arising from clinical diversity (related to participants, interventions and outcomes) and statistical diversity (related to risk of bias) to be present a priori. We quantified statistical heterogeneity by using the I<sup>2</sup> statistic, which reflects the percentage of total variation that is due to heterogeneity rather than to random error.

Publication Bias: We planned to detect publication bias by creating funnel plots for our primary outcomes. As fewer than 10 studies were included (seven included), we were not able to create a funnel plot.

Notes:

CEBM Level of Evidence (Oxford): EL 1 (Systematic review of randomized trials).

Notes:

The authors planned to perform a meta-analysis if heterogeneity was not considerable. However, because of either a small number of studies or heterogeneity, we performed no meta-analyses. Thus the results are reported in a narrative description.

Jiang, H. L. et al. Preoperative use of pregabalin for acute pain in spine surgery: A meta-analysis of randomized controlled trials. *Spine* (Baltimore). 96. e6129. 2017

Evidence level/Study Types P - I - C

Outcomes/Results

<p>Evidence level: 1</p> <p>Study type: SR and META (of 10 RCTs)</p> <p>Databases: PubMed, EMBASE, Web of Science, and Cochrane Database of Systematic Reviews.</p> <p>Search period: September 2016</p> <p>PubMed (1950–September 2016), EMBASE (1974–September 2016), Web of Science (1950–September 2016), and Cochrane Library (September 2016 Issue 3)</p> <p>Inclusion Criteria: RCTs of patients prepared for spine surgery that compared pregabalin with placebo were retrieved</p> <p>Exclusion Criteria: Missing control placebo group.</p>	<p>Population: Adult human subjects (age&gt;18 years) prepared for lumbar surgery (lumbar infusio, lumbar laminectomy, or lumbar discectomy).</p> <p>Intervention: Perioperative pregabalin</p> <p>Comparison: Placebo</p>	<p>Primary: VAS score with rest or mobilization at 12hours, 24hours, cumulative morphine consumption at 24hours and 48hours. Postoperative pain intensity was measured by a 100-point VAS. W rating scale (NRS) was reported, it was converted to a VAS. Addit VAS was converted to a 100-point VAS</p> <p>Secondary: Complications of nausea, sedation, dizziness, hea disturbances (expressed as risk ratio (RR) with 95% CI).</p> <p>Results: 10 clinical studies with 535 patients (pregabalin gr group=241) were included.</p> <p>VAS with rest at 12 h (n=4), 24 h (7), and 48 h (n=4): Preoperative administration of pregabalin can decrease VAS s 12hours (WMD=-1.91, 95% CI -4.07, 0.24, P=0.082). The pregabalin can decrease VAS score with rest at 24hours (WMD=-2 -0.81, P=0.005, Fig. 4) and at 48hours (WMD=-4.33, 95% CI -6.38 -; VAS with mobilization at 12 h (n=3), 24 h (n=4), and 48 h (n=2): There were no significant differences between the pregabalin gro group in the VAS score with mobilization at 12 hours (WMD=-17.8 9.62, P=0.203) and 24hours (WMD=-6.70, 95% CI -14.41, 1.01, P=0 results indicated that there was no significant difference betwee the control group in terms of VAS score with mobilization at 48h 95% CI -11.67, 2.94, P=0.242)</p> <p>Cumulative morphine consumption at 24 h and 48 h: The pooled results indicated that pregabalin can reduce consumption of morphines at 24hours (WMD=-7.07, 95% CI -9.8 and at 48hours (WMD=-6.52, 95% CI -7.78, -5.25, P=0.000)</p> <p>Complications: There were no significant differences between the groups in t sedation (RR=1.17, 95% CI 0.56, 2.42, P=0.679) or headache (RR= 2.08, P=0.540). The NNH for sedation and headache was , respectively. There was no significant difference between th dizziness (RR=1.37, 95% CI 0.90, 2.07, P=0.139) or visual disturbanc (RR=2.00, 95% CI 0.79, 5.02, P=0.142). The NNHfor dizziness was for visual disturbances. Pregabalin can reduce the occurrence of 95% CI 0.41, 0.79, P=0.001) with a significant difference, and the NN Subgroup analysis: low dose of pregabalin (&lt;300mg/d) and a high dose of pregabalin pooled results indicated that a high dose of pregabalin can reduce with rest at 12hours, 24hours, and 48hours with a significant di Both low doses of pregabalin and high doses of pregabalin cumulative morphineconsumption at 24hours and 48hours (P&lt;0.05</p> <p>Author's Conclusion: Preoperative use of pregabalin was efficac of postoperative pain, total morphine consumption, and the occu following spine surgery. Because the sample size and the nu studies were limited, a multicenter RCT is needed to identify the ef dose of pregabalin for reducing acute pain after spine surgery.</p>
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<p><b>Methodical Notes</b></p> <p>Funding Sources: None</p> <p>COI: None</p> <p>Study Quality: The quality was all low risk. The methodological quality of all included trials was independently assessed by Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (<a href="http://www.cochrane-handbook.org/">http://www.cochrane-handbook.org/</a>).</p> <p>Heterogeneity: Statistical heterogeneity was tested using the chi-squared test and I2 statistic. No statistical evidence of heteroge</p> <p>VAS with rest 12h: I2=0.0%, P=0.471  VAS with rest 24h: I2=17.2% P=0.290  VAS with rest 48h: I2=10.1% P=0.351  VAS with mobilization 12h: I2=95.0% P=0.000  VAS with mobilization 24h: I2=63.7% P=0.041  VAS with mobilization 48h: I2=55.7% P=0.133  24h cumulative morphine consumption: I2=60.9% P=0.077  48h cumulative morphine consumption: I2=0.0% P=0.563</p> <p>Publication Bias: Assessed by the funnel plot and quantitatively assessed by Begg's test.  No publication bias between the included studies in terms of VAS score with rest at 12hours, 24hours, and 48hours.</p> <p>Notes:  limitations:  -10 RCTs with relatively small sample size, which might have</p>
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influence on the precision of the final results.

-Follow-up for patients in the included studies ranged from 24hours to 48hours

and this relative short periods follow-up may underestimate the final complications of pregabalin.

-The dosage and interval of pregabalin administration were differ from each studies and thus may cause large heterogeneity

-The different postoperative anesthesia methods (spinal, general, or spinal-epidural) may influence the postoperative pain score large heterogeneity.

-Although publication bias was not detected in Begg's test and this outcome need to treat cautiously since the number of include

Jiang, Y. et al. The efficacy of gabapentin in reducing pain intensity and morphine consumption after breast cancer surgery. *Journal of Clinical Pharmacy and Therapeutics* (Baltimore). 97. e11581. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR and Meta-analysis from RCTs (n=9)</p> <p>Databases: PubMed, Embase, Web of Science, Cochrane Library, Chinese Wanfang databases, and Google databases.</p> <p>Search period: PubMed (1950–November 2017), Embase (1974–November 2017), Web of Science (1950–November 2017), Cochrane Library (November 2017 Issue 3), and Chinese Wanfang databases (1950–November 2017)</p> <p>Inclusion Criteria: RCTs comparing gabapentin with placebo in patients undergoing breast cancer surgery were retrieved.</p> <p>Exclusion Criteria:</p>	<p>Population: Women (age &gt;18 years) undergoing breast cancer surgery</p> <p>Intervention: Perioperative gabapentin</p> <p>Comparison: Placebo</p>	<p>Primary: Visual analog scale (VAS) after surgery and surgery (Postoperative pain intensity was measured by a 110-point numerical rating scale (NRS) was reported, it was converted to a 10-point VAS. Additionally, a 11-point VAS was converted to a 110-point VAS)</p> <p>Secondary: Total morphine consumption, incidence of chronic pain, and the occurrence of nausea. (Opioid drugs were converted to equivalent morphine according to previously published literature (iv morphine 30 mg=iv hydromorphone 1.5 mg=oral hydromorphone 7.5 mg=iv morphine 30 mg=oral oxycodone 20 mg=iv tramadol 100 mg=iv piritramic 30 mg))</p> <p>Results: 9 clinical studies with n= 576 patients (gabapentin group=289).</p> <p>-Sample size ranged from 20 to 50.</p> <p>-Gabapentin doses ranged from 300mg to 1200mg.</p> <p>-Duration of follow-up ranged from 48hours to 6 months</p> <p>VAS after surgery: administration of gabapentin can decrease the VAS score after surgery by 16.14 points (WMD=-16.14, 95% CI -21.85, -10.43, P=.000, low evidence). Middle heterogeneity (I<sup>2</sup>=46.3%, P=.097) between the included studies (n=6).</p> <p>VAS at 24hours after surgery: administration of gabapentin can decrease the VAS score at 24hours after surgery by 27.33 points (WMD=-27.33, 95% CI -33.03, -21.63, P=.000, low evidence). High heterogeneity (I<sup>2</sup>=78.1%, P=.000) between the included studies (n=4)</p> <p>Total morphine consumption: administration of gabapentin can decrease the total morphine consumption after surgery by 4.59mg (WMD=-4.59, 95% CI -7.07, -2.11, P=.000, middle evidence). High heterogeneity (I<sup>2</sup>=78.1%, P=.000) between the included studies (n=4)</p> <p>The occurrence of nausea: administration of gabapentin can decrease the occurrence of nausea after surgery (RR=0.54, 95% CI 0.38, 0.76, P=.000, middle evidence). No heterogeneity (I<sup>2</sup>=0.0%, P=.711) between the included studies (n=4).</p> <p>Chronic pain incidence: administration of gabapentin can decrease the chronic pain incidence (RR=0.57, 95% CI 0.47, 0.68, P=.000, middle evidence). No heterogeneity (I<sup>2</sup>=0.0%, P=.463) between the included studies (n=4).</p> <p>Subgroup analyses were conducted according to a low dose and a high dose of gabapentin (≥900mg/d) (see publication).</p> <p>Author's Conclusion: Immediate and chronic analgesic and opioid-sparing effects were obtained with the administration of gabapentin in breast cancer surgery. Because the sample number of included studies were limited, a multicenter RCT is needed to identify the optimal dose and intervals of gabapentin.</p>

**Methodical Notes**

Funding Sources: This study was funded by National Natural Science Fund regional fund (81760850 and 81660774), Guangxi medical and health appropriate technology research and development project (S201308-03) and Youth Science Foundation of the First Affiliated Hospital of Guangxi University of traditional Chinese Medicine (GZYQJ08).

COI: none

**Study Quality:** -total of 7 items (random sequence generation, allocation concealment, blinding to the participant and person assessing, incomplete outcome, selective reporting, and other bias) were measured  
-Included trials were independently assessed by 2 reviewers using the Cochrane Handbook for Systematic Reviews of Interventions  
-Two reviewers independently evaluated the quality of evidence assessment in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology

**Heterogeneity:** Heterogeneity was tested using the chi-squared test and I<sup>2</sup> statistic.  
No statistical evidence of heterogeneity (I<sup>2</sup><50%, P>.1)

VAS after surgery: middle  
VAS at 24 hours after surgery: high  
Total morphine consumption: high  
The occurrence of nausea: no  
Chronic pain incidence: no

**Publication Bias:** Publication bias was assessed by funnel plot and quantitatively assessed by Begg's test.  
No publication bias: funnel plot was symmetrical and the P value was >.05

**Notes:**  
limitations in this meta-analysis:  
-Only 9 RCTs with small sample (20–50) were included, which might have affected the precision of the effect size estimations.  
-Followup was relatively short and the long-term benefit of gabapentin was unknown.  
-Dosage and timing of gabapentin administration differed between the studies and thus may cause the heterogeneity.  
-Different surgery with or without axillary dissection were included in this meta-analysis, which would cause selection bias.

Jouguelet-Lacoste, J. et al. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a systematic review of the literature. *Pain Med.* 16. 383-403. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level:</b> 2</p> <p><b>Study type:</b> Systematic Review of RCTs (29 trials) The aim of this article is to review the evidence associated with giving low-dose IV infusion of ketamine in the perioperative period for acute pain. Databases: Medline</p> <p><b>Search period:</b> 1966 to November 2013</p> <p><b>Inclusion Criteria:</b> Postoperative inpatient, placebo controlled trials, Route used is IV, Adults, Ketamine alone, PCA IV</p> <p><b>Exclusion Criteria:</b> On anaesthetic hyperalgesia, ICU, No opioids given, Dose above low-dose limit, not appropriate endpoints, not in English, Ketamine not alone, outpatients, not placebo controlled</p>	<p><b>Population:</b> Adults undergoing surgery</p> <p><b>Intervention:</b> Low-Dose intravenous Ketamine</p> <p><b>Comparison:</b> Placebo</p>	<p><b>Primary:</b> Patients opioid consumption, Pain scores</p> <p><b>Secondary:</b> Adverse events and side effects</p> <p><b>Results:</b> Results: Due to length, only summary results are displayed information see full text article. Low-dose IV ketamine reduces opioid consumption by 40%. It also lowers these findings are less clear. No major complications have been reported infusion of ketamine when given up to 48 hours after surgery. While our review using low-dose IV infusion of ketamine in the management of perioperative dose and regimen remain to be determined.</p> <p><b>Author's Conclusion:</b> Thirty-nine clinical trials assessed a continuous infusion of low-dose ketamine for postoperative analgesia using reduction of pain scores as the primary endpoint. The mean reduction of opioid consumption was 40% when using low-dose IV infusion ketamine (infusion rate less than 1.2 mg/kg/h). Ketamine also reduces pain scores, but the amplitude of the effect is less clear. No major complications have been reported with low-dose IV infusion of ketamine following surgery</p>

**Methodical Notes**

**Funding Sources:** Department of Anesthesiology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

COI: None.

**Study Quality:** Quality of the included studies was not investigated.

**Heterogeneity:** No meta-analysis was performed

**Publication Bias:** Not investigated

**Notes:**  
Oxford Level of Evidence: 1 Systematic Review of RCTs (39 trials included)  
Downgrade to Level 2



Quality of the included studies was not rated  
 Publication bias was not investigated  
 Heterogeneity was not analyzed because meta-analysis was not performed  
 Methodology was not presented transparently. Search was only done in a database.

Le Bot, A. et al. Efficacy of intraoperative dexmedetomidine compared with placebo for surgery in adults: a meta-analysis. *Minerva Anestesiologica*. 81. 1105-17. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR and META (of 18 studies)            Databases: Pubmed and Embase.</p> <p>Search period: Until June 2014.</p> <p>Inclusion Criteria: Randomized controlled double blinded studies, presence of a control group and of at least one outcome in relation to intra and/or postoperative analgesia and opioid consumption.</p> <p>Exclusion Criteria: Animal studies were excluded from the search. Patients with established neurological and/or psychiatric diseases, existent standardized protocols for anesthesia and analgesia (including rescue analgesics). Abstracts presented at meetings were not included in the analysis.</p>	<p>Population: Adult surgery.</p> <p>Intervention: Intraoperative and postoperative efficacy of intraoperative Dex administration.</p> <p>Comparison: Placebo.</p>	<p>Primary: Intraoperative opioid consumption, time of recovery from anesthesia (from discontinuation of anesthetics' to comprising extubation), pain during postoperative care (ICU stays (pain scores or percentage of patients with moderate to severe pain), PACU opioid consumption, and prevalence of postoperative nausea or vomiting (PONV) in PACU or ICU.</p> <p>Secondary: See primary.</p> <p>Results: 18 studies were included in the analysis (144 received Dex and 440 received placebos).</p> <p>Intraoperative Dex administration:            - reduced intraoperative opioid consumption (SMD=-1.58 [95% CI -1.85, -1.31], I<sup>2</sup>=95%, P&lt;0.00001), five studies,            - did not decrease time of recovery from anesthesia (SMD=0.13 [95% CI -0.14, 0.34] minutes, I<sup>2</sup>=95%, P&lt;0.00001), 10 studies,            - significantly decreased pain intensity during PACU stay (SMD=-1.19, -0.27], I<sup>2</sup>=62%, P=0.03), 5 studies,            - opioid consumption during PACU or ICU stay (SMD=-1.12], I<sup>2</sup>=83%, P&lt;0.00001), 10 studies, and            - PONV prevalence during PACU stay (OR=0.43 [0.27, 0.66], p=0.46), 10 studies.</p> <p>Subgroup analysis demonstrated that both Dex administration (bolus or continuous infusion with or without bolus) and type of surgery (cardiac, vascular, neurosurgical procedures versus other types of procedures) had an impact on results.</p> <p>Author's Conclusion: In conclusion, results of metaanalysis indicate that intraoperative Dex versus placebo demonstrates intra and postoperative analgesic sparing effect, does not increase time of recovery from anesthesia and reduces PONV in surgical patients.</p>

**Methodical Notes**

Funding Sources: n.a.

COI: Jean Mantz is a member of the Advisory Board of Orion Pharma. The author certifies that there is no conflict of interest regarding the material discussed in the manuscript.

Study Quality: Each reader searched for the presence of potential bias and assessed the quality of the study. Four anesthesiology articles obtained from these queries.

Heterogeneity: Heterogeneity was assessed using I<sup>2</sup> statistics. Given strong heterogeneity in results, subgroup analyzes were performed.

**Publication Bias:** Funnel plot was used to check for publication bias. Three outcomes were examined: time to recovery from consumption in PACU or ICU. No evidence of publication bias was found concerning the first two items. However, potential publication bias in favor of Dex was identified for reduced opioid consumption during PACU or ICU stay.

**Notes:**

CEBM Level of evidenc (Oxford): EL 1 (Systematic review of randomized trials).

**Limitations:**

- high heterogeneity regarding administration and dose of anesthesia, type of surgery and postoperative analgesia protocols
- limited number of studies included for the analysis of each outcome.
- Results concerning postoperative pain and PONV must be interpreted cautiously given the limited validity of scales used for evaluating this outcome.

Li, C. et al. Efficacy of dexmedetomidine for pain management in knee arthroscopy: A systematic review and meta-analysis. *Surg Res.* 12. 49. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> SR and META (5 studies)</p> <p><b>Databases:</b> PubMed, EMBase, Web of science, EBSCO, and the Cochrane library.</p> <p><b>Search period:</b> From inception to March 2017.</p> <p><b>Inclusion Criteria:</b> patients undergoing knee arthroscopy; intervention: dexmedetomidine; control intervention; outcome measure, pain score; and study design, RCT. Conference abstracts meeting the inclusion criteria were also included.</p> <p><b>Exclusion Criteria:</b> none.</p>	<p><b>Population:</b> patients undergoing knee arthroscopy;</p> <p><b>Intervention:</b> dexmedetomidine (concentrations (1-2,5 µg/kg) varied across the included studies). Three studies used intra-articular administration, one i.v. and one administered buccal dexmedetomidine).</p> <p><b>Comparison:</b> control</p>	<p><b>Primary:</b> Pain score or secondary outcomes.</p> <p><b>Secondary:</b> Postoperative diclofenac sodium consumption, duration of effect, hypotension, bradycardia, nausea, and vomiting.</p> <p><b>Results:</b> Pain score: Only two of the included studies reported on primary outcome: pain score. Compared with control group, dexmedetomidine intervention was significantly decreased pain scores (Std. mean difference (SMD)= -0.44; P&lt;.0001 i2="0%," heterogeneity p="0.52)." dexmedetomidine showed significantly reduced postoperative diclofenac sodium consumption (SMD=-1.76; 95% CI=3.32 to 0.21; P=.03, 2 studies) and improved analgesic effect (SMD =1.78; 95% CI=0.56– 3.00; P=.004, four studies) increase in hypotension (RR= 0.93; 95% CI=0.14–5.92; P=.94), bradycardia (RR=0.91–26.58; P=.06), nausea, and vomiting (RR=1.96; 95% CI=0.91–26.58; P=.06).</p> <p><b>Author's Conclusion:</b> Dexmedetomidine showed an important ability to improve duration of analgesic effect in patients undergoing knee arthroscopy. Dexmedetomidine was recommended to be administered for knee arthroscopy, but more studies should investigate the optimal dose and method.</p>

**Methodical Notes**

**Funding Sources:** None.

**COI:** None.

**Study Quality:** Methodological quality: Jadad Scale. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score of 1 was considered low quality. If the Jadad score ≥3, the study was thought to be of high quality. Jadad scores of the 5 included studies varied from 3 to 5. All studies were considered to be high-quality ones according to quality assessment.

**Heterogeneity:** Heterogeneity was tested using the Cochran Q statistic (P<.1 and quantified with the I<sup>2</sup> statistic. an value greater than 50% indicates high heterogeneity.>

**Publication Bias:** Owing to the limited number of included studies (<10) publication bias was not assessed.

**Notes:**

CEBM Level of Evidence (Oxford): EL 1 (Systematic review of randomized trials)

**Limitations:**

- only five studies were included in the analysis despite the small number of inclusion/exclusion criteria
  - all studies comprises few participants (15-30 per group)
  - the doses and administration routs of dexmedetoidine are different
- In conclusion: Due to the above mentioned limitations the relevance of the results is unclear.

Li, F. et al. The efficacy of pregabalin for the management of postoperative pain in primary total knee and hip arthroplasty. *Surg Res.* 12. 49. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results
Evidence level: 1	Population:	Primary: Visual analogue scale (VAS) at 24, 48, and 72 h with rest and at 24 h on

<p><b>Study type:</b> SR and META (of 7 RCTs)</p> <p><b>Databases:</b> PubMed, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar databases.</p> <p><b>Search period:</b> PubMed (1980–July 2016), Embase (1980–July2015)</p> <p><b>Inclusion Criteria:</b> Published RCTs comparing pregabalin with a control (placebo or nothing) in patients who underwent primary TKA or THA are included in this meta-analysis.</p> <p><b>Exclusion Criteria:</b></p>	<p><b>Patients</b> were scheduled for primary TKA and THA</p> <p><b>Intervention:</b> Pregabalin</p> <p><b>Comparison:</b> Placebo or nothing.</p>	<p>morphine consumption.</p> <p><b>Secondary:</b> Knee flexion degree and treatment side effects (nausea, vomit dizziness).</p> <p><b>Results:</b> 823 patients were included from 7 RCTs. The sample sizes for each study were 40 to 216. Four studies were for TKA (n=510), while another three studies were for THA (n=313).</p> <p><b>Morphine consumption (n=6):</b> significant heterogeneity (<math>\chi^2 = 43.57</math>, <math>df = 5</math>, <math>P &lt; 0.001</math>). The pooled results produced a better outcome between the two groups according to the random effects model (MD = -15.92, 95% CI [-26.56–5.29], <math>P = 0.003</math>). A subgroup analysis for the morphine consumption.</p> <p>TKA (n=3) <math>\chi^2=0.34</math> MD and CI (95%) -3.64(-5.04,-2.25) <math>\chi^2(\%)=0</math> <math>P=0.84</math></p> <p>THA (n=3) <math>\chi^2=7.94</math> MD and CI (95%) -22.90(-34.07,-11.74) <math>\chi^2(\%)=75</math> <math>P=0.02</math></p> <p><b>VAS score at rest 24h (n=4):</b> pregabalin produced a better outcome compared with rest at 24 h in terms of VAS score (MD = -0.66, 95% CI [-1.28–0.04], <math>P = 0.04</math>). We used a random effect model because statistical heterogeneity was high (<math>\chi^2 = 14.59</math>, <math>df = 3</math>, <math>P = 0.002</math>, <math>I^2 = 79\%</math>).</p> <p><b>VAS score at rest 48h (n=3):</b> highly significant difference between the two groups (MD = -1.27, 95% CI, [-1.27–0.64], <math>P &lt; 0.00001</math>). A fixed-effect model was preferred because heterogeneity was low (<math>\chi^2 = 0.28</math>, <math>df = 2</math>, <math>P = 0.87</math>, <math>I^2 = 0\%</math>).</p> <p><b>VAS score at rest 72h (n=3):</b> No significant difference between the two groups (MD = -1.42, 95% CI, [-1.42–0.31], <math>P = 0.21</math>). We used a random effect model because of significant heterogeneity (<math>\chi^2 = 7.26</math>, <math>df = 2</math>, <math>P = 0.03</math>, <math>I^2 = 72\%</math>).</p> <p><b>VAS on movement (n=4):</b> No significant difference between the two groups (MD = -0.54, 95% CI, [-1.23–0.15], <math>P = 0.13</math>). The pooled results showed significant heterogeneity (<math>\chi^2 = 6.91</math>, <math>df = 3</math>, <math>P = 0.07</math>, <math>I^2 = 57\%</math>), and therefore, a random effect model was used.</p> <p><b>Knee flexion degree:</b> improved knee flexion degree (see publication)</p> <p><b>Side effect:</b></p> <p><b>Nausea (n=6)</b> Effect: 0.55 CI [0.37, 0.80] <math>p=0.002</math> Heterogeneity: <math>I^2=0</math> <math>P=0.57</math></p> <p><b>Vomits (n=5)</b> Effect: 0.53 CI [0.33, 0.83] <math>p=0.006</math> Heterogeneity: <math>I^2=46</math> <math>P=0.11</math></p> <p><b>Pruritus (n=4)</b> Effect: 0.52 CI [0.29, 0.95] <math>p=0.03</math> Heterogeneity: <math>I^2=0</math> <math>P=1.0</math></p> <p><b>Dizziness (n=4)</b> Effect: 1.95 CI [1.19, 3.18] <math>p=0.008</math> Heterogeneity: <math>I^2=0</math> <math>P=0.75</math></p> <p><b>Author's Conclusion:</b> Our meta-analysis indicated that pregabalin could improve pain control at 24 and 48 h with rest, reduce morphine consumption, and improve the knee flexion as well as decreasing the incident rate of nausea, vomiting, and pruritus and increasing the rate of dizziness after TKA and THA but could not improve the pain control at 72 h. In summary, the use of pregabalin may be a valuable asset in pain management after TKA and THA. However, future studies regarding doses and pregabalin are required.</p>
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**Methodical Notes**

**Funding Sources:** This study was funded by the National Natural Science Foundation of China (NO. 81572154), Tianjin Municipal Health Bureau of Science and Technology Research Projects (15KG123), and Ministry of Medical Health and Health Technology Development Research Center (W2013ZT058).

**COI:** No

**Study Quality:** Methodological quality and risk bias of the included studies were evaluated as follows: (1) randomization method, (2) blinding of participant and outcome assessment, and (3) complete outcome data. The overall methodological quality of the included studies was relatively high. All of the RCTs applied randomized, placebo-controlled strategies, which reflected the high quality of the included literature. Baseline data were provided in all included studies without missing data.

**Heterogeneity:** see results. Statistical heterogeneity was tested using the  $I^2$  value and chi-squared test. A  $P$  value  $<0.05$  was considered significant and the random effect model was used for analysis. If  $P$  values were  $<0.05$  or  $I^2 > 50\%$ , indicating significant heterogeneity, the random effect model was used.

**Publication Bias:** Not shown

**Notes:**  
Oxford level of evidence: 1 Systematic review and meta-analysis  
heterogeneity is high (pooling of different surgeries: TKA and THA)

Li, S. et al. Pregabalin can decrease acute pain and morphine consumption in laparoscopic cholecystectomy randomized controlled trials. *Medicine (Baltimore)*. 96. e6982. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results
Evidence level: 1	Population: Patients who	Primary: Visual analog scale (VAS) score with rest or mobilization at 6, 24, 48, and 72 h and total morphine consumption. Postoperative pain intensity was measured

Study type: SR and META (of 12 RCTs)  
Databases: (PubMed=155, Embase=123, Web of Science=58, Cochrane Library=85, and Google database=114).

Search period: PubMed (1950–March 2017), EMBASE (1974–March 2017), the Cochrane Library (March 2017 Issue 3), and the Google database (1950–March 2017).

Inclusion Criteria: Inclusion criteria in accordance with the PICOS principle. Participants (P): patients who were prepared for laparoscopic cholecystectomy due to cholecystitis; Intervention (I): perioperative oral pregabalin was used as an adjunct to multimodal anesthetics as an intervention group; Comparison (C): placebo; Outcomes (O): visual analog scale (VAS score at 6, 12, and 24hours, total morphine consumption and related complications (nausea, vomiting, dizziness, somnolence, headache, pruritus, urinary retention, respiratory depression, and blurred vision); Study design (S): RCTs.

Exclusion Criteria:

were prepared for laparoscopic cholecystectomy due to cholecystitis.

Intervention: Perioperative oral pregabalin was used as an adjunct to multimodal anesthetics.

Comparison: Placebo

110-point VAS (0=no pain and 100=extreme pain). When the numerical r reported, it was converted to a VAS. Additionally, a 10-point VAS was 110-point VAS.

Secondary: Morphine-related complications (i.e., nausea, vomit somnolence, headache, pruritus, urine retention, respiratory depression, vision.

Results:

Ultimately, 12 clinical studies with 938 patients (gabapentin group=402) were included in the metaanalysis.

VAS scores with rest at 6, 12, and 24hours: Postoperative VAS scores at 12hours were reported in 3 studies, and the pooled results indicated that preoperative administration of pregabalin can decrease the VAS score at 6hours (WMD=-11.27, 95% CI -16.92, -5.62, P=.000). The postoperative VAS scores at 12hours in the included studies had a large heterogeneity ( $I^2=96.4\%$ ), required a random-effect model that was performed to analyze the data, and Begg's tests (P=.722) were performed, and the results indicated that there was no publication bias between the included studies in terms of the VAS score. A sensitivity analysis was then conducted to analyze the source of heterogeneity between the studies, and the results indicated that none of the included studies affected the results. The meta-analysis results indicated that gabapentin can decrease the VAS score at 12hours (WMD=-9.46, 95% CI -18.13, -0.79, P=.032). Postoperative VAS scores at 12hours in the included studies had a large heterogeneity ( $I^2=98.3\%$ ), required a random-effect model to be performed to analyze the relevant data. The analysis results indicated that gabapentin can decrease VAS scores at 12hours (WMD=3.99, 95% CI 6.80, 1.19, P=.005). Postoperative VAS scores at 6hours in the included studies had a large heterogeneity ( $I^2=67.3\%$ ), which required a random-effect model to be performed to analyze the relevant data. VAS scores with mobilization at 6, 12, and 24hours.

VAS scores with mobilization at 6, 12, and 24hours: Postoperative VAS scores with mobilization at 12hours were reported in 3 studies, and the pooled result indicated that the preoperative administration of pregabalin can decrease the VAS score with mobilization at 6hours (WMD=-8.74, 95% CI -13.07, -4.42, P=.000). The postoperative VAS scores with mobilization at 6hours in the included studies had a large heterogeneity ( $I^2=34.1\%$ , P=.000), which required a random effect model to be performed to analyze the data. The meta-analysis results indicated that pregabalin can decrease the VAS score with mobilization at 12hours (WMD=-5.80, 95% CI -10.26, -1.34, P=.000). Postoperative VAS with mobilization at 12hours in the included studies had a large heterogeneity ( $I^2=43.4\%$ , P=.171), which required a random-effect model to be performed to analyze the relevant data. The meta-analysis results indicated that pregabalin can decrease the VAS score with mobilization at 24hours (WMD=-11.80, 95% CI -16.92, -6.68, P=.021). The postoperative VAS scores with mobilization at 24hours in the included studies had a large heterogeneity ( $I^2=59.0\%$ , P=.087), which required a random-effect model to be performed to analyze the relevant data. A scatter plot was generated to show the relationship. We plotted the pregabalin dose on the abscissa and the VAS score with rest at 6, 12, and 24hours on the ordinate to generate a scatter plot. In addition, the linear correlation coefficient (r) was calculated. There was a negative correlation between the dosage of pregabalin and the VAS score at 6hours (r=-0.31, P=.031). There was no correlation between the dosage of pregabalin and the VAS score with rest at 12hours (r=-0.437, P=.139) and 24hours (r=-0.496, P=.211).

Total morphine consumption: Total morphine consumption was present in all studies. One study adopted 4 different doses of gabapentin compared to a placebo, consequently divided into 4 groups. The pooled results indicated that pregabalin can reduce total morphine consumption (WMD =-168.60, 95% CI -231.78, -105.42, P=.000).

Complications: There were no significant differences between the occurrence of nausea (RR=0.60, 95% CI 0.42, 0.88, P=.157, NNT=1.57), respiratory depression (RR=0.17, 95% CI 0.03, 0.90, P=.017, NNT=8.02), pruritus (RR=1.16, 95% CI 0.30, 4.52, P=.853, NNT=13.5), dizziness (RR=1.61, 95% CI 0.76, 3.38, P=.212, NNT=4.61), blurred vision (RR=1.01, 95% CI 0.74, 1.38, P=.953, NNT=190.88), or headache (RR=1.01, 95% CI 0.74, 1.38, P=.953, NNT=190.88).

Subgroup analyses: Subgroup analyses were conducted according to a low dose of gabapentin (<300mg/d) and a high dose of gabapentin (≥300mg/d). The detailed results are shown in publication Table 2. The pooled results indicated that a high dose of gabapentin can reduce the VAS score with rest at 6, 12, and 24 hours and nausea and vomiting compared to a low dose (P<.05). The other outcomes were all associated with a high dose of gabapentin thus data insufficient to perform subgroup analyses.

**Author's Conclusion:** In conclusion, pregabalin was efficacious in the postoperative pain, total morphine consumption and morphine-related side effects following laparoscopic cholecystectomy. In addition, a high dose of pregabalin was more effective than a low dose. The dose of pregabalin differed across studies and the heterogeneity was large. More high quality studies are needed to evaluate the optimal dose of pregabalin in laparoscopic cholecystectomy patients.

**Methodical Notes**

**Funding Sources:** None reported

**COI:** None

**Study Quality:** The reliability of the study selection was determined by Cohen's kappa test, and the acceptable threshold was a kappa value regarding the evaluation of the risk of bias of included RCTs was 0.815, which indicates that the agreement between reviewers was good. Quality of all included trials was independently assessed by 2 reviewers on the basis of the Cochrane Handbook for Systematic Reviews version 5.1.0. A total of 7 domains were used to assess the overall quality as follows: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Evidence was classified as low bias, unclear bias, or high bias.

Subgroup analysis was conducted according to the dose of pregabalin (<300mg/d or ≥300mg/d).

**Heterogeneity:** Statistical heterogeneity was evaluated using the I<sup>2</sup> test and the I<sup>2</sup> statistic.

**Publication Bias:** Publication bias was tested using funnel plots and Begg's test. We considered that no publication bias occurred if the plot was symmetrical, and the P-value in Begg's test was >.05.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

Li, Y. Z. et al. Subarachnoid and epidural dexmedetomidine for the prevention of post-anesthetic shivering: a meta-analysis. *Drug Des Devel Ther.* 13. 3785-3798. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> SR and META (of 22 studies)</p> <p><b>Databases:</b> PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials.</p> <p><b>Search period:</b> Inception - Dec. 2017.</p> <p><b>Inclusion Criteria:</b> (1) RCTs; (2) adults older than 18 years who were categorized as ASA I-III and underwent selective surgery under spinal anesthesia, epidural anesthesia or combined spinal-epidural anesthesia; (3) DEX was administered via subarachnoid space route (SSR) or epidural space route (ESR); (4) only saline was used as the placebo in the control group and (5) binary data on shivering were available or the available data could be transferred into binary data.</p> <p><b>Exclusion Criteria:</b> use of serotonin receptor agonists, central analgesics, opioids or opioid derivatives; outpatient surgery within 2 hrs; patient with neuromuscular disease, hypothalamus or spinal injury or contraindication to DEX or S&amp;E anesthesia; incomplete reports; and an incorrect statistical approach.</p>	<p><b>Population:</b> Adults with selective surgery.</p> <p><b>Intervention:</b> Injection of DEX was over SSR (14 studies) and ESR (3 studies). Via SSR, most implementations were at a dosage of ≤5 µg (15) while others received &gt;5 µg.</p> <p><b>Comparison:</b> Saline as control group.</p>	<p><b>Primary:</b> presence of shivering - defined as any visible muscle tremors.</p> <p><b>Secondary:</b> Side effects (bradycardia, hypotension, nausea, vomiting, ...), sedation and block information.</p> <p><b>Results:</b> Primary outcome - shivering</p> <p>Two studies reported post-anesthetic shivering on a shivering scale and 1 study reported on a 3-point scale. Others treated post-anesthetic shivering as a secondary outcome with no clear definition.</p> <p>22 studies with 1389 patients reported on shivering.</p> <p>The incidence of post-anesthetic shivering decreased from 20.10% in the control group to 10.30% in the experimental group (RR, 0.48; 95% CI, 0.39-0.59; Z=6.86, P&lt;0.00001, I<sup>2</sup>=92%). Subgroup analysis showed no significant difference in the incidence of shivering between the control and experimental groups in either surgical category or drug administration route.</p> <p>In the SSR subgroup, a dosage of &gt;5 µg showed a superior shivering effect than that of ≤5 µg (RR, 0.23, 0.60; 95% CI, 0.09-0.49 and 0.40-0.90 respectively; I<sup>2</sup>= 78.9%).</p> <p><b>Secondary outcomes:</b></p> <p><b>Bradycardia:</b> 12 studies_797 patients: The incidence of bradycardia increased from 5.84% in the control group to 10.30% in the DEX group (RR, 2.49; 95% CI, 1.45- 4.28; Z=3.30, P&lt;0.00001, I<sup>2</sup>= 92%).</p> <p><b>Hypotension:</b> 10 studies_646 patients: The incidence of hypotension increased from 14.89% in the control group to 27.42% in the DEX group (RR, 2.38; 95% CI, 0.76-7.64; Z=3.30, P&lt;0.00001, I<sup>2</sup>= 92%).</p> <p><b>Nausea and vomiting:</b> 19 studies_1189 patients: The incidence of nausea and vomiting decreased from 10.54% in the control group to 7.95% in the DEX group (RR, 0.81; 95% CI, 0.58-1.15; Z=1.15, P=0.24, I<sup>2</sup>=0%).</p> <p><b>Duration of analgesia:</b> 12 studies_711 patients: This showed S&amp;E DEX prolonged the time of the patient receiving first analgesic rescue (SMD, 4.43; 95% CI, 3.00-5.86; Z=11.15, P&lt;0.00001, I<sup>2</sup>=97%).</p> <p><b>Author's Conclusion:</b> In this study, we demonstrate that the adjuvant drug, prophylactic S&amp;E DEX attenuates PAS. M</p>

a dose of >5 µg over SSR has a better anti-shivering effect than a dose of ≤5 µg. However, this is not applicable to meperidine at high concentrations or outpatients. This conclusion should be interpreted cautiously when patients have an underlying condition such as bradycardia.

**Methodical Notes**

**Funding Sources:** National Natural Science Foundation of China (81471448) and the Natural Science Foundation of Zhejiang Province. The sponsors had no involvement from study design to submission of the paper for publication.

**COI:** none.

**Study Quality:** Risk of bias for the 22 studies is considerably low (Cochrane risk of bias tool). The quality of evidence was (RRPAS<0.5) and dose–response gradient. The final evidence level was high. The evidence recommendation was strong for the net benefits.

**Heterogeneity:** See results.

**Publication Bias:** A funnel plot revealed visual symmetry after excluding the study of Shahi et al.- Shai is the only study reporting Dex administration.

**Notes:**  
CEBM Level of Evidence: EL 1 (Systematic review of randomized trials)

**Notes/Limitations:**  
 - The authors stated in the discussion: The greatest concern regarding the off-label administration route of DEX is its neurotoxicity. Was DEX used off-label in this review?!  
 - small sample groups (20-50 patients/group)  
 - shivering was reported by visual inspection not instrument detection  
 - majority of the studies was conducted in India/China; thus the generalization of the findings may be limited.

Li, Z. et al. Ketamine reduces pain and opioid consumption after total knee arthroplasty: A meta-analysis of randomised controlled trials. *British Journal of Plastic Surgery*. 70. 70-83. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> Systematic Review and Meta-Analysis of RCTs (6 trials, 244 patients) To examine the analgesic efficacy and safety of ketamine after total knee arthroplasty.</p> <p><b>Databases:</b> Pubmed, Embase, Ovid, Cochrane Library, Web of Science, CNKI, Wanfang Data, VIP</p> <p><b>Search period:</b> Inception to February 2019</p> <p><b>Inclusion Criteria:</b> Studies were chosen for meta-analysis if they met the following criteria: Population: patients with knee osteoarthritis scheduled for TKA. Intervention: TKA with ketamine for pain management. Comparison: TKA without ketamine. Outcomes: postoperative pain score at 6–48 h, morphine consumption, length of hospitalization and adverse effects. Study design: RCTs.</p> <p><b>Exclusion Criteria:</b> Studies were excluded if any of the following existed: low-quality RCTs and non-RCTs, undefined sample and control sources, nontherapeutic clinical studies, nonoriginal studies, non-full-text reports, and undefined grouping.</p>	<p><b>Population:</b> Patients with knee osteoarthritis scheduled for TKA</p> <p><b>Intervention:</b> TKA with ketamine for pain management</p> <p><b>Comparison:</b> TKA without ketamine</p>	<p><b>Primary:</b> Postoperative pain score at 6–48 h, morphine consumption, length of hospitalization and adverse effects.</p> <p><b>Secondary:</b></p> <p><b>Results:</b> <u>Results:</u> Only summary results are displayed. For further information see full text article. A total of six randomized controlled trials were included in the meta-analysis. The present meta-analysis demonstrated significant differences between the two groups in pain score within the first 24 postoperative hours, morphine consumption, and length of hospitalization. Notably, ketamine could significantly reduce the incidence of nausea and vomiting without increasing the incidence of thrombosis.</p> <p><b>Author's Conclusion:</b> Ketamine is effective in reducing cumulative morphine consumption during the early postoperative period after total knee arthroplasty. In addition, ketamine is associated with a lower incidence of adverse effects.</p>

**Methodical Notes**

**Funding Sources:** None.

**COI:** None.

**Study Quality:** Two authors independently assessed the methodological quality of the included studies through using of the Cochrane collaboration's tool

for assessing the risk of bias

**Heterogeneity:** Heterogeneity was examined using the I2 statistic. Studies with an I2 of 25%–50% were considered to possess moderate heterogeneity, and a random effect model was used. I2 > 50% was considered to be of a high heterogeneity, and a random effect model was used. If not assessed, P < 0.05 was considered statistically significant.

**Publication Bias:** Not assessed (less than 10 trials included)

**Notes:**

**Oxford Level of Evidence:** 1 Systematic Review and Meta-Analysis of RCTs (6 trials, 244 patients)

Overall the number of included trials and patients was small, which may lead to overestimation of treatment effects.

High heterogeneity was present for the main outcomes: Painscore at 24 h (I2 = 71,4%), Cumulative morphine consumption at 24h (I2 = 96,8%), likely due to differences among the administration of ketamine in the trials but limits the generalizability of the findings.

**Liu, B. et al. A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain. Journal of Clinical Pharmacy and Therapeutics (Baltimore). 96. e8031. 2017**

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> SR and META (of 12 RCTs)</p> <p><b>Databases:</b> PubMed, EMBASE, Web of Science, Cochrane Library, and Google databases.</p> <p><b>Search period:</b> PubMed (1950–March 2017), EMBASE (1974–March 2017), Web of Science (1950–March 2017), Cochrane Library (September 2017 Issue 3), and Google database (1974–March 2017).</p> <p><b>Inclusion Criteria:</b> Adults (age &gt;18 years) undergoing lumbar surgery (lumbar fusion, lumbar laminectomy, or lumbar discectomy).</p> <p><b>Exclusion Criteria:</b></p>	<p><b>Intervention:</b> Perioperative gabapentinoids as an intervention group.</p> <p><b>Comparison:</b> Placebo</p>	<p><b>Primary:</b> Visual analogue scale (VAS) score with rest or mobilization at 6, 12, 24, and 48hours and cumulative morphine consumption at 24 and 48hours</p> <p><b>Secondary:</b> Complications of nausea, vomiting, sedation, dizziness, headache retention, pruritus, and visual disturbances.</p> <p><b>Results:</b> Sixteen clinical studies (gabapentin group n=8 and pregabalin group n=8).</p> <p><b>VAS with rest at 6, 12, and 24 hours:</b> Postoperative VAS scores at 6hours were reported in 16 studies, and the pooled results indicated that preoperative administration of gabapentinoids was associated with reduced VAS at 6, 12, 24, and 48hours corresponding to a reduction of 10.57 points (WMD=-10.57, 95% CI -14.52, -6.63, P=0.000), 9.29 points (WMD=-9.29, 95% CI -11.74, -6.85, P=0.000) at 12hours and 7.19 points (WMD=-7.19, 95% CI -10.45, -3.93, P=0.000) at 24hours (WMD=-7.19, 95% CI -10.45, -3.93, P=0.000) on a 110-point visual analogue scale.</p> <p><b>Cumulative morphine consumption at 24 and 48 hours:</b> The pooled results indicated that gabapentinoids can reduce the cumulative consumption of morphine at 24hours (WMD=-18.55, 95% CI -23.52, -13.57, P=0.000). Because only the patients in the pregabalin group reported the cumulative consumption of morphine, pooled results suggest that pregabalin can reduce the cumulative consumption of morphine at 48 hours (WMD=-7.78, 95% CI -5.25, P=0.000).</p> <p><b>Complications:</b> There were no significant differences between the groups in the occurrence of sedation (RR=1.29, 95% CI 0.73, 2.28, P=0.541). Gabapentinoids significantly reduce the occurrence of nausea (RR=0.69, 95% CI 0.54, 0.88, P=0.000). Gabapentinoids can also significantly reduce both the occurrence of vomiting (RR=0.34, 95% CI 0.34, 0.76, P=0.004) and pruritus (RR=0.34, 95% CI 0.22, 0.55, P=0.001).</p> <p><b>Subgroup analysis:</b> Subgroup analysis was based on the dose of pregabalin (&lt;300mg/d was identified as low dose, while ≥300mg/d was identified as high dose) and gabapentinoids (&lt;900mg/d was identified as low dose, while ≥900mg/d was identified as high dose). Subgroup analysis was also performed based on the category of the drugs (gabapentinoids and pregabalin). Subgroup analyses were conducted based on the dose and timing of administration of gabapentinoids; Subgroup results indicated that pregabalin was superior to gabapentinoids in reducing both acute pain and cumulative morphine use at 24 and 48hours. Furthermore, a high dose of gabapentinoids was superior to a low dose of gabapentinoids in reducing acute pain and cumulative morphine consumption following spinal surgery.</p> <p><b>Author's Conclusion:</b> This is the first meta-analysis to compare the preoperative use of gabapentinoids versus a placebo for the management of pain after spine surgery. Analgesic efficacy and opioid-sparing effects were observed with the administration of gabapentinoids. Additionally, a significant decrease in the risk of nausea, vomiting, and pruritus was associated with the use of gabapentinoids. The optimal dose and timing of administration of gabapentinoids will require further study.</p>

**Methodical Notes**

**Funding Sources:** None reported

**COI:** None

**Study Quality:** The methodological quality of all included trials was independently assessed by 2 reviewers using the Cochrane Reviews of Interventions, version 5.1.0. A total of 7 items (random sequence generation, allocation concealment, blinding to blinding to the outcome assessment, incomplete outcome, selective reporting, and other bias) were measured. The risk of bias of random sequence generation showed unclear risk of bias in 4 studies. Only 1 study failed to describe the personnel, and 2 studies had unclear risk of bias for blinding of the outcome assessment. The remaining studies all exhibited overall risk of bias for all studies was low.

**Heterogeneity:** Statistical heterogeneity was tested using the  $\chi^2$  test and I<sup>2</sup> statistic. No statistical evidence of heterogeneity (I<sup>2</sup> reduced the level of evidence was the heterogeneity between the studies, which was caused by the different doses and time used. The type of gabapentinoids was also a source of heterogeneity. In the end, we performed a subgroup analysis to reduce the

**Publication Bias:** Publication bias was tested using funnel plots. Publication bias was assessed by funnel plot and quantitatively considered there to be no publication bias if the funnel plot was symmetrical and the P value was  $> .05$ . No potential publication bias between the VAS at 6 hours. The P value obtained from the Begg test was .903.

**Notes:**  
Oxford level of evidence: 1 Systematic review and meta-analysis

Mao, Y. et al. The efficacy of preoperative administration of gabapentin/pregabalin in improving pain after total hip arthroplasty. *BMC Musculoskelet Disord.* 17. 373. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> Systematic Review and Meta-Analysis of RCTs (7 trials, 769 patients) The purpose of this systematic review and meta-analysis of randomised controlled trials (RCTs) was to evaluate the pain control by gabapentin or pregabalin administration versus placebo after total hip arthroplasty (THA). <b>Databases:</b> Medline, Embase, PubMed, CENTRAL (Cochrane Controlled Trials Register), Web of Science and Google</p> <p><b>Search period:</b> Inception to January 2016</p> <p><b>Inclusion Criteria:</b> (1) randomised controlled trials (RCTs); (2) patients who underwent a primary THA; (3) interventions, including gabapentin or pregabalin, versus control (placebo or nothing); and (4) reported outcomes, including postoperative VAS pain with rest or mobilisation at 24 and 48 h, cumulative morphine consumption at 24 and 48 h as well as the incidence of pruritus, vomiting, dizziness, and nausea. The article needed to include at least one of the outcomes mentioned above</p> <p><b>Exclusion Criteria:</b> We excluded studies of cadavers or artificial models. We also excluded non-RCTs, letters, comments, editorials, practice guidelines and other studies with insufficient data.</p>	<p><b>Population:</b> Patients who underwent a primary THA</p> <p><b>Intervention:</b> Gabapentin or pregabalin</p> <p><b>Comparison:</b> Placebo or nothing</p>	<p><b>Primary:</b> Postoperative VAS pain with rest or mobilisation cumulative morphine consumption at 24 and 48 h as well as pruritus, vomiting, dizziness, and nausea.</p> <p><b>Secondary:</b></p> <p><b>Results:</b> <u>Results:</u> Due to length only summary results are displayed. For further information see full text article. Seven studies involving 769 patients met the inclusion criteria. Treatment with gabapentin or pregabalin can decrease morphine consumption at 24 h (mean difference (MD) = -7.82; -0.52; P &lt; 0.001) and 48 h (MD = -6.90; 95 % CI -0.95 to -12.85; P &lt; 0.001). Gabapentin or pregabalin produced no better outcome than placebo at 24 h (SMD = 0.15; 95 % CI -0.17 to 0.48; P = 0.11) or at 48 h (SMD = 0.22; 95 % CI -0.25 to 0.69; P = 0.363). There was no significant difference between the groups with respect to VAS score with rest at 24 h (SMD = 0.46; 95 % CI -0.19 to 1.11; P = 0.001) or postoperatively (SMD = 1.15; 95 % CI -0.58 to 2.89; P = 0.001). Gabapentin or pregabalin decreased the occurrence of nausea (relative risk (RR), 0.49; 95 % CI 0.025 to 0.95; P = 0.001), but there was no significant difference in the incidence of dizziness and pruritus.</p> <p><b>Author's Conclusion:</b> On the basis of the current meta-analysis, gabapentin or pregabalin can decrease the cumulative morphine consumption and the occurrence of nausea; however, further trials are needed to assess the effect of pain control by gabapentin or pregabalin.</p>

**Methodical Notes**

**Funding Sources:** None.

**COI:** None.

**Study Quality:** The risk of bias for each RCT was evaluated using the Cochrane Collaboration's Risk of Bias Tool.

**Heterogeneity:** Statistical heterogeneity was tested using the chi-squared test and I<sup>2</sup> statistic. A chi-squared test scoring I<sup>2</sup> > 50% indicated the presence of statistical heterogeneity. When there was no statistical evidence of heterogeneity, a fixed effects model was adopted; otherwise, a random effects model was chosen.

Heterogeneity was present for the main outcomes: 24 h cumulative morphine consumption (I<sup>2</sup>=87,2%), 48 h cumulative morphine consumption (I<sup>2</sup>=87,2%), 24 h VAS with rest (I<sup>2</sup>=87,2%), 48 h VAS with rest (I<sup>2</sup>=87,2%), 24 h VAS with mobilisation (I<sup>2</sup>=87,2%), 48 h VAS with mobilisation (I<sup>2</sup>=87,2%), 24 h pruritus (I<sup>2</sup>=87,2%), 48 h pruritus (I<sup>2</sup>=87,2%), 24 h vomiting (I<sup>2</sup>=87,2%), 48 h vomiting (I<sup>2</sup>=87,2%), 24 h dizziness (I<sup>2</sup>=87,2%), 48 h dizziness (I<sup>2</sup>=87,2%).



score with rest at 24 h (I<sup>2</sup>=63,7%), VAS score with rest at 48 h (I<sup>2</sup>=78%), VAS score with mobilization at 24 h (I<sup>2</sup>=91%), VAS score with mobilization at 48

**Publication Bias:** Publication bias was tested by Begg's test and was none if the P value obtained from Begg's test is greater than 0.1. Begg's funnel plot is approximately asymmetrical and thus indicated that there is no publication bias between the included studies. P = 0.133, Fig. 4).

**Notes:**

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs ( 7 trials, 769 patients)

Quality of the included studies was rated as high by the authors.

Publication bias is approximately not present.

Heterogeneity was present for the main outcomes: 24 h cumulative morphine consumption (I<sup>2</sup>=87,2%), 48 h cumulative morphine consumption (I<sup>2</sup>=87,2%), VAS score with rest at 24 h (I<sup>2</sup>=63,7%), VAS score with rest at 48 h (I<sup>2</sup>=78%), VAS score with mobilization at 24 h (I<sup>2</sup>=91%), VAS score with mobilization at 48 h (I<sup>2</sup>=97,8%). Therefore the implications of this article for practice are limited.

**Mishriky, B. M. et al. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. *Journal of Clinical Pharmacy and Therapeutics*. 2015; 40(1): 31-41.**

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level: 1</b></p> <p><b>Study type:</b> Systematic Review and Meta-Analysis of RCTs (55 trials, 4155 patients)</p> <p>Therefore, we performed this systematic review to provide an updated meta-analysis of the impact of pregabalin administration on postoperative pain scores and opioid consumption and investigate whether those outcomes differ according to individual pregabalin dose, frequency of administration, type of anaesthesia, or type of surgery. Secondary aims were to assess the impact of pregabalin administration on anxiety scores and persistent pain, and provide an updated meta-analysis of the side-effects of pregabalin administration</p> <p><b>Databases:</b> Medline, Cochrane Register of Controlled Trials, Embase, Cinahl</p> <p><b>Search period:</b> Inception to 2014</p> <p><b>Inclusion Criteria:</b> Articles were included if pregabalin was administered before operation and pain scores, opioid consumption, incidence of persistent pain, and/or time to first analgesia were reported.</p> <p><b>Exclusion Criteria:</b> We excluded studies where pregabalin administration was initiated after operation, the endpoints of interest were not reported or if a placebo group was not included.</p>	<p><b>Population:</b> Patients undergoing surgery</p> <p><b>Intervention:</b> Pregabalin was administered before operation</p> <p><b>Comparison:</b> Placebo</p>	<p><b>Primary:</b> Pain scores and opioid consumption at 2 and 24 h.</p> <p><b>Secondary:</b> Duration of PACU and hospital stay, incidence of persistent pain at 2 and 12 months, preoperative anxiety scores, and side-effects.</p> <p><b>Results:</b> Results: Only summary results are displayed here due to limited information see full text article. When all doses and administration regimens were combined, pregabalin was associated with a significant reduction in pain scores at rest and during movement at 24 h compared with placebo {mean difference (95% CI) = 20.38 (20.57, 20.20), 20.47 (20.76, 20.18), and 28.2 (210.08, 26.47), respectively}. Patients receiving pregabalin had less postoperative nausea and vomiting and pruritus compared with placebo (RR (95% CI) = 0.62 (0.48, 0.80) and 0.49 (0.34, 0.70), respectively). Side effects and visual disturbance were more common with pregabalin compared with placebo (95% CI) = 1.46 (1.08, 1.98), 1.33 (1.07, 1.64), and 3.52 (2.05, 6.04), respectively. Doses of pregabalin tested (≤75, 100–150, and 300 mg) resulted in opioid consumption after surgery. There were no significant differences in acute pain scores between pregabalin 100–300 mg between single preoperative dosing regimens including additional doses repeated after surgery. Data were insufficient to draw conclusions regarding persistent pain, but limited data available suggested that pregabalin might be effective for the reduction of neuropathic pain.</p> <p><b>Author's Conclusion:</b> In conclusion, this review suggests that pregabalin provides postoperative analgesia compared with placebo at the expense of increased side effects and visual disturbances.</p>

**Methodical Notes**

**Funding Sources:** This article was supported solely by departmental funds.

**COI:** None.

**Study Quality:** The articles meeting the inclusion criteria were assessed separately by two authors (B.M.M. and N.H.W.) using the Cochrane Collaboration.

**Risk of bias assessment** indicated that most included studies had a low risk of bias

**Heterogeneity:** We assessed heterogeneity using the I<sup>2</sup> -test. Heterogeneity was assumed to be present if the I<sup>2</sup> was >50%.

High heterogeneity was present for the main outcomes: Pain scores at 2h at rest (I<sup>2</sup>=88%) and at movement (I<sup>2</sup>=82%), Pain scores at 24h at rest (I<sup>2</sup>=70%), Opioid consumption at 2h (I<sup>2</sup>=94%) and at 24h (I<sup>2</sup>=95%).

**Publication Bias:** We assessed for publication bias for the primary outcomes using the Egger's test.

There was no evidence of publication bias for pain scores at rest or movement (P=0.07 and 0.71, respectively). There was no evidence of publication bias for opioid consumption at rest or movement (P=0.13 and 0.13, respectively).

(P=0.94 and 0.65 for pain scores at rest and on movement, respectively). There was no evidence of publication bias for opioid 24h (P=0.21)

**Notes:**

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (55 trials, 4155 patients)

Results are based on a large number of included studies and patients

High heterogeneity was present for then main outcomes likely due to different types of surgery and patients, different pregabalin types and different regimens (single and multiple dosing) included, limits the implication for practice.

No evidence for publication bias was present.

Overall the risk of bias of the included studies was rates as low by the authors.

Pan, L. et al. The efficacy of ketamine supplementation on pain management for knee arthroscopy: A meta-analysis of Medicine (Baltimore). 98. e16138. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (7 RCTs, 300 patients)</p> <p>To compare the efficacy of ketamine supplementation versus placebo for knee arthroscopy.</p> <p>Databases: Pubmed, Embase, Web of science, EBSCO, Cochrane library databases</p> <p>Search period: Inception to October 2018</p> <p>Inclusion Criteria: The inclusive selection criteria are as follows: population: patients undergoing knee arthroscopy; intervention: ketamine supplementation; comparison: placebo; study design: RCT.</p> <p>Exclusion Criteria: Not described</p>	<p>Population: Patients undergoing knee arthroscopy</p> <p>Intervention: Ketamine supplementation</p> <p>Comparison: Placebo</p>	<p>Primary: Pain scores within 2 hours</p> <p>Secondary: Analgesic consumption, time to first analgesic requirement, malondialdehyde vomiting.</p> <p>Results: Results: Only summary results are displayed here due to length, for further in text article</p> <p>Seven RCTs involving 300 patients are included in the meta-analysis. Overall, compared v for knee arthroscopy, ketamine supplementation reveals favorable impact on pain scores [MD]=-2.95; 95% confidence interval [CI]=-3.36 to -2.54; P&lt;.00001 analgesic consumption mean difference md ci="-1 time first requirement and malondialdehyde shows no increase in nausea vomiting&gt;</p> <p>3.11 Author conclusions</p> <p><b>B</b></p> <p><b>k</b></p> <p><b>u</b></p> <p>tief</p> <p>hoch</p> <p>≤</p> <p>≥</p> <p>≠</p> <p>≈</p> <p>←</p> <p>→</p> <p>↔</p> <p>μ</p> <p>±</p> <p>&lt;br&gt;&lt;br&gt;</p> <p><b>Author's Conclusion:</b> Ketamine supplement benefits to pain management and may reduce ischemia reperfusion injury with knee arthroscopy</p>

**Methodical Notes**

**Funding Sources:** Not described.

**COI:** None.

**Study Quality:** Methodological quality of the included studies is independently evaluated using the modified Jadad scale.[19] T randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). The score of Jadad Scale varies from 0 to 5. A Jadad score  $\leq 2$  is considered to be of low quality. If the Jadad score  $\geq 3$ , the study is thought to be of high quality.

**Heterogeneity:** A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I<sup>2</sup> statistic, and heterogeneity. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting 1 study or performing subgroup analysis.

**Publication Bias:** Not analyzed (less than 10 trials included)

**Notes:**

**Oxford Level of Evidence:** 1 Systematic Review and Meta-Analysis (7 RCTS, 300 patients)

Analysis is based on 7 RCTs, and all of them have a relatively small sample size ( $n < 100$ ). These may lead to overestimation of effects.

Methodology partly intransparently (e.g. description of the exclusion criteria is missing, detailed results of the quality assessment are missing).

**Paramasivan, A. et al. Intrathecal dexmedetomidine and postoperative pain: A systematic review and meta-analysis of Eur J Pain. 24. 1215-1227. 2020**

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> SR and META (24 RCTs included)</p> <p><b>Databases:</b> Medline (through Ovid), EMBASE (through Ovid), The Cochrane Library, Web of Science, Turning Research into Practice (TRIP), PubMed, Clinicaltrials.gov and International Clinical Trials Registry Platform (ICTRP). Google Scholar was searched from 2010 to January 2019. In addition, the reference lists of included articles were also hand-searched.</p> <p><b>Search period:</b> From inception until January 2019.</p> <p><b>Inclusion Criteria:</b> Adult patients, elective surgery under spinal anaesthesia, intrathecal DEX (any dose/volume) vs. placebo (normal saline), humans, RCTs.</p> <p><b>Exclusion Criteria:</b> Studies in children, patients having nonelective surgery, studies that did not report the postoperative analgesic duration and pain scores, and those that did not provide sufficient data for analysis.</p>	<p><b>Population:</b> Adult patients undergoing elective surgery under spinal anaesthesia. In total of 1,460 patients from the 24 RCTs were included: 769 patients were assigned to the DEX group and 691 to the placebo group (A total of 427 were assigned to other comparator groups, which included clonidine, buprenorphine, midazolam and neostigmine and were not included in the analysis).</p> <p><b>Intervention:</b> Intrathecal DEX (any dose/volume)</p> <p><b>Comparison:</b> Placebo (normal saline)</p>	<p><b>Primary:</b> Postoperative analgesic duration, defined as intrathecal injection to the time of first complain administration of rescue analgesia.</p> <p><b>Secondary:</b> (a) pain scores measured by a 10-cen analogue scale (VAS) or 10-point numeric rating scale and 24 postoperative hours and (b) the rate of tre adverse effects such as postoperative sedation, nausea shivering, hypotension and bradycardia.</p> <p><b>Results:</b> Hyperbaric bupivacaine (63%) and isobaric bup were the most commonly used LA agents. The doses DEX ranged from 2 mcg to 20 mcg, with the most administered dose being 5 mcg (64%). The most common rescue analgesics were diclofenac (50%) and tramadol (3</p> <p><b>Median postoperative analgesic duration</b> was significantly prolonged in the DEX group (363.6 min (range 204.0-824.0)) compared to the placebo group (204.0 min (range 120.0-824.0)) with substantial heterogeneity (<math>I^2 = 98\%</math>). But an overall effect was recognizable.</p> <p><b>Postoperative Pain score:</b> 8 studies At 24 postoperative hours, patients in the DEX group reported a mean pain score difference of 1 point less (out of a maximum of 10) compared to the placebo group (95% CI -1.9, -0.20; significant difference at other time points (6 and 12h) with heterogeneity <math>&gt;94\%</math>).</p> <p><b>Adverse events:</b> There were no statistically significant differences in the incidence of hypotension, bradycardia and nausea and vomiting between the intrathecal DEX and placebo group. The incidence of shivering was significantly lower in patients who received intrathecal DEX compared to those in the placebo group (pooled RR 0.58, 95% CI 0.34–0.98, <math>p = 0.04</math>).</p> <p><b>Author's Conclusion:</b> In conclusion, this meta-analysis comprising 1,460 patients undergoing spinal anaesthesia for various types of surgeries showed that intrathecal DEX significantly prolonged postoperative analgesic duration when compared with placebo and also marginally reduced pain scores at 24 hr. There were no adverse effects when compared with LA alone. Intrathecal DEX is considered a safe option for patients undergoing surgeries with postoperative pain particularly those intolerant of systemic analgesics. However, the optimal dose of intrathecal DEX for different types of surgeries as well as its long-term neurological effects warrants further research.</p>

**Methodical Notes**

**Funding Sources:** For this review: n.a.  
for included RCTs: The source of funding was unknown in 14 studies and no funding was given for the remaining 10 studies.

**COI:** None

**Study Quality:** Sixty-seven percent of the studies were assessed to have a low risk of bias in more than three domains. The remaining 33% were unclear or high risk of bias in three or more domains.

**Heterogeneity:** Asymmetry was observed due to the heterogeneity of the studies and the lack of studies with larger sample sizes. The results were observed when performing subgroup analyses for different dosages of drugs used or sensitivity analysis by removing studies with high or unclear risk of bias.

**Publication Bias:** Authors stated: Publication bias is also a factor as all the RCTs were conducted in Asian and Middle Eastern countries which may have differing pharmacogenetic profiles and pain thresholds, limiting its generalizability to other populations. The lack of Agency (EMA) approval for intrathecal DEX may have prevented the approval of RCTs in other countries. DEX is currently used for sedation, but there is mention of intranasal, subcutaneous, perineural, buccal and intrathecal use in multiple studies worldwide.

**Notes:**

Oxford Level of evidence: EL 1 (systematic review of randomized trials)

**Limitations:**

- small sample size in all included studies
- significant heterogeneity (authors stated that this may be because of:
  - a) the different LA agents used, (b) the differing criteria to evaluate postoperative analgesic duration (c) the different types of surgery (d) the variable duration of surgery (weighted mean duration range 26.5–172.8 min) and (e) the different primary outcomes.
- DEX is not approved by FDA and European Medicines Agency (EMA) for intrathecal administration.

**Pendi, A. et al. Perioperative Ketamine for Analgesia in Spine Surgery: A Meta-analysis of Randomized Controlled Trials. E299-E307. 2018**

**Evidence level/Study Types**

**P - I - C**

**Outcomes/Results**

**Evidence level:** 1

**Study type:** Systematic Review and Meta-Analysis of RCTs (14 trials, 649 patients)  
To evaluate the effectiveness of perioperative supplemental ketamine to reduce postoperative opioid analgesic consumption following spine surgery

**Databases:** Pubmed, Cochrane Central Register of Controlled Trial for prospective randomized controlled trials (RCTs), Web of Science, Scopus

**Search period:** Not described

**Inclusion Criteria:** (1) the article described a human study; (2) ketamine was administered; (3) elective, inpatient spine surgery was performed; (4) the article described a randomized controlled trial; (5) postoperative analgesia was reported; (6) postoperative pain scores were reported (6) postoperative complications were reported; (7) general anesthesia was administered.

**Exclusion Criteria:** (1) the article described a non-human study; (2) ketamine was only administered for general anesthesia; (3) trauma, outpatient, or non-spine surgery were conducted; (4) the article did not describe a

**Population:**  
Patients undergoing spine surgery

**Intervention:**  
Patients that received supplemental ketamine

**Comparison:**  
Saline

**Primary:** Postoperative opioid consumption, postoperative pain scores, adverse effects

**Secondary:**

**Results: Results**  
A total of 14 RCTs comprising 649 patients were selected for inclusion into the metaanalysis. Patients that were administered supplemental ketamine exhibited less cumulative morphine equivalent consumption at 4 (MD: -5.69, 95% CI: -10.73 to -0.65, p=0.03), 8 (MD: -8.10, 95% CI: -10.54 to -5.78, p<0.001), 12 (MD: -7.06, 95% CI: -12.99 to -1.13, p=0.02) and 24 hours (MD: -14.38, 95% CI: -18.13 to -10.62, p<0.001) following spine surgery. The ketamine group also reported lower postoperative pain scores at 6 (MD: -1.18, 95% CI: -1.67 to -0.69, p<0.001), 12 (MD: -1.01, 95% CI: -1.51 to -0.52, p<0.001), and 24 hours (MD: -1.27, 95% CI: -1.70 to -0.84, p<0.001). None of the events studied attained statistical significance (all ps>0.05).

**Author's Conclusion:** Supplemental perioperative ketamine significantly reduced postoperative opioid consumption up to 24 hours following spine surgery.

clinical trial; (5) postoperative analgesia was not reported; (6) postoperative pain scores were not reported; (7) general anesthesia was not administered; (8) a treatment or control arm of the trial comprised 10 patients or fewer; (9) non-English language article.

**Methodical Notes**

Funding Sources: None.

COI: None.

Study Quality: Quality of the included studies was not investigated.

Heterogeneity: Chi-squared analysis was used to test for heterogeneity between studies with a significance value set at 0.10 in significant heterogeneity. Heterogeneity was further quantified by applying the I<sup>2</sup> test with values exceeding 50% indicating heterogeneity. The random effects model was used to incorporate between studies heterogeneity for comparisons with phetero! model was used.

Morphine equivalent consumption at 12 hours (I<sup>2</sup>=97%), Morphine equivalent consumption at 24 hours (I<sup>2</sup>=78%), Morphine equi (54%), Postoperative pain scores at 12 hours (I<sup>2</sup>=97%), Postoperative pain scores at 24 hours (I<sup>2</sup>=62), Postoperative pain scores

Publication Bias: Publication bias was not investigated

Notes:

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (14 trials, 649 patients)

Downgrading to Level 2

High heterogeneity was present for all of the main outcomes. Therefore the implication of this article is limited.

Quality of evidence was not investigated.

Methodological intransparency: search period, control group, outcomes were not or not sufficiently described

Rai, A. S. et al. Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients underg systematic review and meta-analysis of randomized controlled trials. J Plast Reconstr Aesthet Surg. 70. 1317-1328. 201

**Evidence level/Study Types**

**P - I - C**

**Outcomes/Results**

Evidence level: 1

Study type: SR and META (of 4 RCTs)  
Databases: MEDLINE, EMBASE, CENTRAL, Web of Science, and ProQuest, clinical trial registry (www.clinicaltrials.gov) and reference lists of all eligible trials. Open Access, Theses and Dissertations and ProQuest Dissertations and Theses for any eligible unpublished.

Search period: Inception of each database through November 2015.

Inclusion Criteria: all perioperative interventions for acute and chronic pain used in breast cancer surgery in adult patients.

Exclusion Criteria:

Population: Included studies enrolling adult patients undergoing breast cancer surgery who were randomly assigned to preoperative

Intervention: Pregabalin

Comparison: Placebo

Primary: Acute pain (in the recovery room and at 24 h post chronic pain (>2 months postoperatively). Acute pain scores were converted from individual studies t rating scale for pain.

Secondary: postoperative morphine consumption and adv postoperative nausea and vomiting). opioid consumption was converted into parenteral morphin using previously published opioid conversion tables.

Results: 4 pregabalin trials (n=209)

Postoperative pain (n=2):

One trial reported on pain scores in the recovery room significant reduction in pain intensity in the pregabalin g difference at rest, p=0.01 for difference on movement). scores at 24 h postoperatively among these two studies significant reduction with pregabalin use (MD=-0.38, 95% p=0.21, I<sup>2</sup>=0%, moderate QoE).

Opioid consumption (n=3):

Among the pregabalin studies, three trials reported on opi in the recovery room, and their pooled results demonstra reduction in parenteral morphine-equivalent consumption 95% CI -8.76 to -0.83, p=0.02, I<sup>2</sup>=88%, low QoE) Only one t 24-h opioid consumption and reported a significant decre consumption in the pregabalin group (92.86 mg in the p versus 162.50 mg in the placebo group, p=0.029).

Chronic pain (n=2):

two pregabalin trials reported on persistent postoperative there was no effect of pregabalin on reducing chronic pain 0.23, 95% CI 0.02 to 2.80, p=0.25, I<sup>2</sup>=85%, very low QoE)

Adverse events (n=4):

Two of the trials reported greater somnolence in the prega in the placebo group. Two trials reported on postopera vomiting, with both studies reporting a greater number of a the placebo group. No statistical differences were observe

dizziness, blurred vision, or drowsiness reported in the study groups receiving pregabalin and placebo groups.

**Author's Conclusion:** Pregabalin reduces pain in the reduction of opioid consumption but not pain at 24 h. We found low-to-moderate quality evidence that neither drug affects the development of CFA. Large RCTs are needed to provide conclusive data regarding the role of perioperative gabapentin for women undergoing surgery for breast cancer.

**Methodical Notes**

**Funding Sources:** none

**COI:** none

**Study Quality:** The overall risk of bias across included trials was low, and most trials (3 of 4) were at low risk of bias for all domains.

**Heterogeneity:** Heterogeneity was assessed by using the I<sup>2</sup> statistic. Significant heterogeneity associated with some of our pooled results could not be explained as the distribution of available trials failed to meet our threshold for subgroup analysis based on risk of bias categories.

**Publication Bias:** not applied

**Notes:**

Bewertung nur für Pregabalin, Gabapentin siehe Doppelpublikation (Jiang 2018)

Ren, Y. et al. Efficacy of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia in abdominal randomised controlled trials. *Int Wound J.* **16.** 1206-1213. 2019

**Evidence level/Study Types**

**P - I - C**

**Outcomes/Results**

**Evidence level:** 1

**Study type:** Systematic review and meta-analysis: 5 studies  
"To evaluate effects of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia in abdominal surgery."  
**Databases:** MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.

**Search period:** Inception - November 2018.

**Inclusion Criteria:** (a) RCTs, (b) local wound infiltration was performed before or after operation, (c) adult patients (≥18 years old), (d) the experimental group included the comparison of DEX with local anaesthetics and local anaesthetics alone, at least, (e) abdominal operation, including minimally invasive surgery and open surgery, and (f) availability of full-text publication in English.

The operation technique, the dosage of DEX, and the dosage and type of local anaesthetics were not considerations for inclusion.

**Exclusion Criteria:** (a) were abstracts only, (b) were duplications, (c) had data loss, and (d) inaccurate statistical analysis was performed in the study.

**Population:** Patients undergoing abdominal operations (open and laparoscopic)

**Intervention:** Dexmedetomidine (DEX) as an adjuvant to local wound infiltration anaesthesia.

**Comparison:** local anaesthetics and local anaesthetics alone.

**Primary:** Postoperative pain (VAS score at 6, 12, 24h post-operative).

**Secondary:** Total analgesic consumption 24h after surgery. Incidence of postoperative nausea and vomiting (PONV) 24h after surgery.

**Results:** Results: only summary results presented here, rest see article controlled trials (RCTs) involving 294 patients were included. Then, 10 patients were excluded from the studies and their effect sizes were calculated using the Cochrane Manager 5. As a result, the addition of DEX significantly reduced visual analogue scores at 6 hours after surgery (mean difference = -0.53 [-0.82, -0.25], P < .001), at 12 hours after surgery (mean difference = -0.39 [-0.73, -0.05]; P = .03), and 24 hours after surgery (mean difference = -0.20 [-0.29, -0.11], P < .001) and reduced analgesic consumption within 24 hours after surgery (mean difference = -4.92 [-5.18, -4.66], P < .001) compared with placebo groups. However, there was no difference in the incidence of postoperative nausea and vomiting (risk ratio = 0.68 [0.41, 1.14]; P = .09). DEX as a local anaesthetic adjuvant added for local wound infiltration anaesthesia in abdominal surgery could reduce visual analogue scores and postoperative analgesic consumption without changing incidence of postoperative nausea and vomiting.

**Author's Conclusion:** "In conclusion, DEX as a local anaesthetic adjuvant added for local wound infiltration anaesthesia in abdominal surgery could reduce postoperative opioid consumption without changing the incidence of PONV. However, more large-sample and high-quality RCTs are needed to increase the certainty of evidence in the current metaanalysis."

**Methodical Notes**

**Funding Sources:** "This study was supported by the National Natural Science Foundation of China (81800395) and Science and Technology Innovation Project of the Chinese Academy of Sciences (2016YFA0100900)." (Jiang 2018)

Henan Province (182102310159)  
National Natural Science Foundation of China, Grant/Award Number: 81800395; Science and Technology Department of Henan 182102310159"

COI: No conflicts of interest declared.

**Study Quality:** All the selected documents were reviewed by two reviewers to evaluate the methodological quality of the included studies using the Cochrane Collaboration's risk of bias assessment tool. They evaluated the quality of each article from the random method, the blind law of the research objects and the implementers, the blind method of the results measurement, the integrity of the report, report bias, and the other bias sources. Finally, the low-bias, high-bias, and unclear judgments were obtained. When they discussed the disagreements to reach consensus or the issue was decided by two other reviewers.

**Heterogeneity:** The Q ( $\chi^2$ ) test and I2 statistics were used for assessing the studies' heterogeneity. If the P value for the Q test was considered not significant the fixed-effects model was used otherwise we assumed that there were random-effects to calculate effect sizes. Sensitivity analysis analysed sources of heterogeneity.>

**Publication Bias:** Not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Publication bias not investigated. High heterogeneity in some of the results (PONV 24h)

Riddell, J. M. et al. Low-dose ketamine in painful orthopaedic surgery: a systematic review and meta-analysis. *Br J Anaesth* 2018; 121: 100-110.

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level: 1</b></p> <p><b>Study type:</b> Systematic Review and Meta-Analysis of RCTs (20 trials, 1271 patients) The objective of this systematic review was to critically appraise the evidence from RCTs that used low-dose ketamine in adult patients undergoing pain orthopaedic procedures. <b>Databases:</b> Medline, Embase, Cochrane Library, Web of Science, Biosis, ASA abstracts, Cinahl, ClinicalTrials.gov, WHO trials</p> <p><b>Search period:</b> Inception to July 2018</p> <p><b>Inclusion Criteria:</b> We considered parallel-design RCTs of low-dose/microdose ketamine in major orthopaedic surgical procedures occurring in the operating room, excluding crossover or cluster randomised trials.</p> <p><b>Exclusion Criteria:</b> Excluding crossover or cluster randomised trials. Unpublished studies were evaluated if there was sufficient evidence to warrant their inclusion. We excluded studies that did not involve orthopaedics, studies that used ketamine as an induction agent, and paediatric studies. Studies that used ketamine at doses outside the specified ranges were excluded. Emergency room studies were excluded if they did not lead to a procedure in the operating room. If the surgical procedure was not explicitly stated, the study was excluded. We also excluded studies if their full texts were unavailable.</p>	<p><b>Population:</b> Excluding crossover or cluster randomised trials. Unpublished studies were evaluated if there was sufficient evidence to warrant their inclusion. We excluded studies that did not involve orthopaedics, studies that used ketamine as an induction agent, and paediatric studies. Studies that used ketamine at doses outside the specified ranges were excluded. Emergency room studies were excluded if they did not lead to a procedure in the operating room. If the surgical procedure was not explicitly stated, the study was excluded. We also excluded studies if their full texts were unavailable.</p> <p><b>Intervention:</b> Patients received low-dose ketamine as: 1. An IV bolus (0.1-0.5 mg/kg), before or during the procedure. 2. An infusion of 1-10 µg kg<sup>-1</sup>min<sup>-1</sup>, terminated at any point 48 h afterwards. 3. Some combination of a bolus and an infusion.</p> <p><b>Comparison:</b> Excluding crossover or cluster randomised trials. Unpublished studies were evaluated if there was sufficient evidence to warrant their inclusion. We excluded studies that did not involve orthopaedics, studies that used ketamine as an induction agent, and paediatric studies. Studies that used ketamine at doses outside the specified ranges were excluded. Emergency room studies were excluded if they did not lead to a procedure in the operating room. If the surgical procedure was not explicitly stated, the study was excluded. We also excluded studies if their full texts were unavailable.</p>	<p><b>Primary:</b> 1. The total amount of opioid (µg) used by patients after operation either by nurses (intravenous and oral) or part of patient-controlled analgesia devices. 2. The time to the first dose of opioid after surgery (minutes). A longer period to receive the first dose was considered indicative of poor pain control. 3. The pain scores at rest using the visual analogue scale (VAS) at 12, 24, and 48 hours. In certain studies, the 11-point Numerical Rating Scale (NRS) was used, where the score stated a value for their pain without a visual representation. Studies that did not demonstrate a correlation between pain scores and one can reliably be substituted for the other. Although some studies involved pain scores with movement, pain at rest was widely reported, so only those at rest were analysed.</p> <p><b>Secondary:</b> 1. The effect of ketamine on the incidence of postoperative nausea and vomiting (PONV). 2. The incidence of hallucinations. 3. Whether or not patients developed pain after surgery, defined as: a. pain developed after a surgical procedure that lasted greater than 2 months' duration. b. causes of pain had been ruled out.</p> <p><b>Results:</b> We included 20 studies across 10 subgroups for meta-analysis. The quality of the evidence was high. Ketamine significantly decreased the amount of opioid used and pain scores (VAS) at 24 hours (Opioid: standardised mean difference -0.82 [-1.24, -0.40], p=0.0001, a 50% reduction; VAS: SMD -0.40 [-1.03,-0.27], p=0.0008; VAS: SMD -0.15, p=0.006 and -0.60 [-1.00,-0.20], p=0.008), and delayed the time to first dose (SMD 0.64 [0.01, 1.27], p=0.05) for nausea and hallucinations were not significant, whereas results for chronic pain were inconclusive. The most prominent adverse effects were seen in total joint operations.</p> <p><b>Author's Conclusion:</b> Low-dose ketamine is an effective adjuvant that decreases</p>

opioid requirements in painful or procedures, especially in the first procedure. Future research should arthroscopic procedures and the inc chronic pain.

**Methodical Notes**

Funding Sources: None.

COI: None.

Study Quality: We used the Cochrane criteria to assess the risk of bias, and we rated the overall body of evidence using the GRADE. The two authors (JMR, JMT) independently assessed the risk of bias, and disagreements were resolved through consensus. If no consensus was reached, the third author (IJO) arbitrated.

Heterogeneity: We assessed heterogeneity using the I<sup>2</sup> statistic; values of 25%, 50%, and 75% represented mild, moderate and high heterogeneity respectively.

Publication Bias: We used funnel plots to assess publication bias

Notes:

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (20 trials)

Overall the quality of the included studies was moderate.

High heterogeneity was present for the main outcomes (opioid use 12h I<sup>2</sup>=91%, opioid use 24h I<sup>2</sup>=88%, opioid use 48h I<sup>2</sup>=83%, pain scores at 24h I<sup>2</sup>=83%). Therefore the implications of this review is limited.

Sanchez Munoz, M. C. et al. What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials. *Anesth.* **38**. 140-153. 2017

**Evidence level/Study Types**

**P - I - C**

**Outcomes/Results**

Evidence level: 1

Study type: SR and META (16 trials for quantitative analysis).  
Databases: PubMed/Medline and the Cochrane database.

Search period: 1966 – November 2014

Inclusion Criteria: Human randomized controlled trials involving adults (aged >18 years) who received systemic (oral, intramuscular, transdermal and intravenous) clonidine pre, per or postoperative undergoing local, regional or general anesthesia for every type of surgery, testing its different effects. Only publications in English were included.

Exclusion Criteria: Studies with no appropriate data reporting (e.g. size effect in term of mean response) were excluded from the quantitative analyses, and, eventually, from the qualitative analyses. Incomplete or unclear reports were excluded.

Population: Adults who received clonidine pre, per or postoperative undergoing local, regional or general anesthesia for every type of surgery.

Intervention: see inclusion criteria

Comparison: see inclusion criteria

Primary: At least one of the following.  
First analgesic intake/time to first analgesic;  
Pain scores at 24 h ;  
Analgesic consumption at 24 h ;  
Postoperative nausea and vomiting prevention;  
Bleeding control;  
Inhalatory induction time;  
Heart rate reduction after tracheal intubation (1 min);  
Mean arterial pressure reduction after tracheal intubation (1 min);  
Hormonal and catecholaminergic stability;  
Preoperative oxygen consumption reduction;  
Intraoperative oxygen consumption reduction;  
Postoperative oxygen consumption reduction;  
Increased diuresis ;  
Decreased renin activity;  
Shivering incidence reduction;  
Shivering treatment;  
Sedation and anxiolysis;  
Patients'satisfaction;  
Cardiac protection.

Secondary: see primary.

Results: We analyzed 57 trials concerning 14,790 patients (ASA aged between 18 and 93) of whom 7408 received clonidine (100 µg/kg), 6836 received placebo, 501 received others drugs and 45 were excluded.

Postoperative analgesia were reported in 10 trials including 412 patients (209 received clonidine, 299 placebo, 20 melatonin and 29 were excluded). First analgesic intake/time to first analgesic (FAI/ TAR) were reduced and pain scores (visual analgesic scale, VAS, at 12, 24 and 48 h) were reduced. Pain scores at rest were not reduced in the majority of the studies (Variability in scales types not suitable for quantitative analysis). In contrast, cumulative analgesic consumption was reduced at 24 h and 36 h. Four trials were included in the quantitative analysis showing a reduction of analgesics consumption after 24 h (relative risk [95%CI][16%–32%])(p < 0.001). Data of PONV were reported in 6 trials including 412 patients (209 received clonidine, 181 placebo, 36 midazolam and 15 were excluded). PONV was significantly reduced by clonidine in all the 6 trials (relative risk [95%CI][0.25–0.51])(p < 0.001).

Data of anesthetics-sparing effect were reported in 18 trials including 14,790 patients (540 received clonidine, 497 placebo, 50 received diazepam or metoprolol and 8 were excluded).



Anesthetics consumption was reported in 18 trials. Anes significantly reduced in all the trials. Regarding heterogeneity of we did not perform any quantitative analysis.

Data of shivering were reported in 7 trials. In 5 of the trials cloni prophylaxis, including 660 patients (330 received clonidine a incidence of shivering was significantly reduced in the 5 t shivering was reported in the 2 trials reporting it. Three trials we quantitative analysis, showing a reduction of the incidence of sh 0.17, 95%CI[0.10–0.29]; p < 0.001).

For other outcomes see text.

**Author's Conclusion:** In conclusion, these systematic review a of 57 trials shows that clonidine improves pain control, reduces hemodynamic and sympathetic stabilities, with no adverse c renal function or awakening time, but does not influence cardia general population after non-cardiac surgery. Nevertheless, heterogeneity between the studies, this does not exclude di patient subgroups or specific procedures. Further research may candidates (patients) for clonidine indications, and on the way t to the patients and the procedure.

**Methodical Notes**

**Funding Sources:** None.

**COI:** None.

**Study Quality:** The Cochrane Collaboration's tool was used for assessing risks of bias at the study level (including funnel plots)

**Heterogeneity:** Heterogeneity was assessed by the I2 statistics for each comparison. An I2 N>40% was considered to reject the (and to accept heterogeneity hypothesis).

**Publication Bias:** Funnel plots were used to analyze a potential publication bias and no evidence of such bias was founded.

**Notes:**

CEBM Level of Evidence (Oxford): EL 1 (Systematic review if randomized trials).

**Sanders, J. G. et al. Gabapentin for Perioperative Analgesia in Otorhinolaryngology-Head and Neck Surgery: Systema Neck Surg. 155. 893-903. 2016**

**Evidence level/Study Types**

**P - I - C**

**Outcomes/Results**

**Evidence level:** 1

**Study type:** Systematic review (15 studies)  
To identify whether sufficient evidence exists for the routine use of gabapentin in the perioperative setting.

**Databases:** MEDLINE, EMBASE, Google Scholar, and the Cochrane Central Register of Controlled Trials.

**Search period:** Inception - 11 / 2015

**Inclusion Criteria:** Included studies were randomized controlled trials (RCTs) involving human surgical patients of all ages in whom gabapentin (experimental intervention group) was administered perioperatively for ORL-HNS procedures and compared with either placebo or an active control. Trials were required to include data in the form of pain scores, analgesic consumption, or adverse effects of gabapentin (eg, dizziness, sedation). English-language publications were considered.

**Exclusion Criteria:** not specified.

**Population:** Otorhinolaryngology–Head and Neck Surgery patients

**Intervention:** Gabapentin (experimental intervention group) was administered perioperatively

**Comparison:** Placebo or an active control

**Primary:** Pain intensity score.

**Secondary:** Analgesic consumption and adverse ef

**Results:** Only summary results displayed due to see article.

"A total of 14 randomized controlled trials were which 4 had an active control. The placebocon included 4 for tonsillectomy, 3 for rhinology, thyroidectomy. These studies were not suitabl analysis. Trial quality involving gabapentin in t surgery is variable. The higher-quality studi significantly reduced analgesic consumption in th groups, with the effect on pain scores less clear. significant benefit, within the first 24 hours, analgesic consumption as compared with placebo gabapentin groups following rhinologic and thyroid

**Author's Conclusion:** "A single preoperative dose c appears to have a significant effect in reducing p pain and analgesic consumption as compared v during the first postoperative day in ORL-HNS Preoperative gabapentin reduces postoperative pai analgesic consumption within the first 24 hours fo surgery and thyroidectomy. A reduction in consumption was also present with gabapentin ir hours following tonsillectomy. However, its postoperative pain scores is less clear. Further clin required to determine the impact of gabapentin on postoperative pain and analgesic use afte operations."

**Methodical Notes**

**Funding Sources:** New Zealand Lottery Health Research Board Grant, which had no influence on the study design and from which research reporting

**COI:** None.

**Study Quality:** Included studies were allocated a quality score via the validated 3-item scale described by Jadad et al<sup>13</sup> (Table of bias in pain research reports based on randomization, blinding, withdrawals, and dropouts. The higher the score, the less the Of 4 active-controlled trials reporting postoperative tonsillectomy pain, 3 had low quality scores (Jadad score, 2 of 5).

**Heterogeneity:** No meta-analysis was performed. "Limitations pertinent to this review include not undertaking a meta-analysis; variation in Jadad scores of the studies included."

**Publication Bias:** Not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

Low quality of included studies. Selection, extraction, assessment of studies was likely only performed by a single investigator.

Sun, R. et al. Intra-articular clonidine for post-operative analgesia following arthroscopic knee surgery: a systematic review. *Surg Sports Traumatol Arthrosc.* 22. 2076-84. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 2</p> <p>Study type: SR and META (7 studies). Databases: PubMed, EMBASE, Cochrane Library, ISI Web of knowledge and Chinese Biomedical Literature Database. Google Scholar and other databases were also searched.</p> <p>Search period: From their start year up to March 2012.</p> <p>Inclusion Criteria: No restrictions were imposed on language. RCTs comparing single dose of IA clonidine with placebo for post-operative pain following arthroscopic knee surgery were included. Additional interventions with placebo effect will be allowed, if received equally by all intervention and control groups.</p> <p>Exclusion Criteria: Duplicate publications were excluded.</p>	<p>Population: Arthroscopic knee surgery was conducted during general anaesthesia, and IA solution was restricted to be injected into articular cavity right after the surgery.</p> <p>Intervention: Single dose of IA clonidine (all except one study applied Clonidine with 150 µg IA).</p> <p>Comparison: Placebo.</p>	<p>Primary: Post-operative pain intensity was the most important outcome (All pain scores on a VAS from 0 to 10 were adjusted to a scale of 0 to 10).</p> <p>Secondary: Supplementary analgesics (time to first analgesia, total rescue analgesic consumption and total number of pain rescue analgesics) and adverse effects (operative nausea, vomiting, sedation, hypotension, bradycardia).</p> <p>Results: Seven studies with 230 patients were included.</p> <p>Pain intensity: Six studies reported VAS scores after surgery. The results of meta-analysis showed that, placebo, IA clonidine reduced the pain intensity significantly at 1, 2, 4 and 24 h after surgery. There were no significant differences, however, were found for pain scores at 6 and 12 h.</p> <p>Supplementary analgesic use: Reduced the risk of using rescue analgesics (heterogeneity, no pooling possible).</p> <p>Adverse effects: The results of meta-analysis showed that clonidine increased the incidence of hypotension, however, there were no significant differences between clonidine and placebo for total adverse effects.</p> <p>Author's Conclusion: A single dose of IA clonidine had a definite analgesic effect, but the analgesic effect was short lasting, which is just for 4 h after IA clonidine alone could not provide adequate post-operative analgesia following arthroscopic knee surgery. Post-operative hypotension may be the side effect that should be paid the most attention in clinical setting.</p>

**Methodical Notes**

**Funding Sources:** n.a.

**COI:** none.

**Study Quality:** Cochrane Collaboration's risk of bias tool: moderate risk of bias.

Heterogeneity: Heterogeneity of the studies was evaluated using the  $I^2$  test and the  $I^2$  statistic,  $I^2 > 50\%$  was considered to be significant for heterogeneity, and the reason for heterogeneity was explored.

Publication Bias: n.a.

Notes:

CEBM Level of Evidence (Oxford). EL 1 (systematic review of randomized trials). Downgraded one Level to EL 2 because of meth

This review includes studies published between 1996 and 2006, thus the relevance may be limited.

In addition, only seven studies were included.

There was high heterogeneity between the studies regarding rescue analgesic, time to first analgesia, outcomes of pain intensity to 25 per group) in the included studies was low, so the impact of the review is unclear.

Tsaousi, G. G. et al. Dexmedetomidine as a sedative and analgesic adjuvant in spine surgery: a systematic review and controlled trials. *Eur J Clin Pharmacol.* 74. 1377-1389. 2018

Evidence Types	level/Study	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR and META (15 studies, whereas only 8 were included in the qualitative analysis)</p> <p>Databases: PubMed, EMBASE, Cochrane Central Register of Controlled Trials and International Web of Science databases.</p> <p>Search period: From inception to 10. March 2018</p> <p>Inclusion Criteria: RCTs (1) adult patients (age <math>\geq 18</math> years) undergoing elective or emergency spine surgery; (2) RCTs involving the perioperative use of DEX either as a sedative and analgesic adjuvant (experimental group), compared to placebo or active comparators (control group); (3) provision of data with respect to at least one of the primary outcome measures up to 48 h postoperatively; and (4) availability of full text publication in English language.</p> <p>Exclusion Criteria:</p>	<p>Population: Administration of DEX in patients undergoing surgery for all types of spine pathology (with the exception of scoliosis surgery).</p> <p>Intervention: Perioperative use of DEX either as a sedative and analgesic adjuvant.</p> <p>Comparison: Placebo or active comparators.</p>	<p>Primary: Sedative and analgesic efficacy of DEX assessed by either consumption of supplementary anesthetic or analgesic modalities or scores between study groups.</p> <p>Secondary: Perioperative hemodynamic performance, intraoperative recovery from anesthesia (quality and time to awakening), and the occurrence of events such as postoperative nausea or vomiting (PONV), somnolence, dizziness, respiratory depression, urine retention or other rare side effects</p> <p>Results: In total 913 patients were included (n= 415 Dex group and n= 498 placebo group). 8 studies comprises placebo as control group. With the exception of Garg et al. and Terao et al. who applied DEX only for sedation, all the selected studies involved the administration of DEX in a setting as an adjunct to general anesthesia or for conscious sedation in spine surgery cases.</p> <p>DEX administration followed a standard pattern (in most studies a combination of a bolus dose (0.3 <math>\mu\text{g}/\text{kg}</math> to 1 <math>\mu\text{g}/\text{kg}</math>) delivered over 10-15 minutes subsequent maintenance infusion (0.2 <math>\mu\text{g}/\text{kg}/\text{h}</math> to 0.6 <math>\mu\text{g}/\text{kg}/\text{h}</math>).</p> <p>DEX-treated patients showed a significant reduction of both propofol [MD, -214.47 mg; 95%CI, -253.16 to -175.78; <math>P &lt; 0.001</math>] and morphine consumption both intraoperatively and postoperatively (MD, -2.69; 95%CI, -2.33; <math>P &lt; 0.001</math> and MD, -4.36 mg; 95%CI, -6.93 to -1.79; <math>P &lt; 0.001</math>) compared to those assigned to placebo. Postoperative nausea and vomiting were comparable between DEX and placebo groups, whilst other adverse effects were not consistently reported.</p> <p>Author's Conclusion: In conclusion, DEX emerges as an attractive alternative to standard sedative and analgesic modalities applied in spine surgery. Moreover, DEX seems to offer satisfactory control of pain and reduce analgesic requirements in the postoperative period. These properties are coming along with an enhanced safety profile as from the available evidence no clear hemodynamic compromise or any other adverse effects can be documented.</p>	

#### Methodical Notes

Funding Sources: n.a.

COI: None.

Study Quality: Quality: Jadad scale.

Only three RCTs were of poor quality due to the absence of data regarding randomization method or blinding.

Risk of bias: Cochrane risk of bias tool.

The risk of bias estimation revealed that most of the studies enrolled are characterized by moderate to low risk of bias.

Heterogeneity: Between-study heterogeneity was assessed with the Cochrane Q test using a  $\chi^2$  function ( $P$  values less than 0.05). Within-group heterogeneity was quantified using the  $I^2$  statistic. For substantial heterogeneity ( $I^2 > 50\%$ ), a random-effect model was used in the analysis, otherwise, a fixed-effect model was applied.

Publication Bias: Funnel plot, if at least 10 studies can be included in the META-analysis. n.a. because only 8 studies were included.

Notes:

CEBM Level of Evidence: EL 1 (Systematic review of randomized trials).

**Limitations:**

- dosage regimen varied considerably among the included RCTs, as well as the intraoperative and postoperative analgesic modalities...
- relevance of results unclear due to the high diversity of above
- authors stated, much of the available data are in minor spine procedures while those supporting the use of DEX in major spine

Ul Huda, A. et al. Pre-medication with Gabapentin is associated with significant reductions in nausea and vomiting after shoulder arthroscopy: a meta-analysis. *Orthop Traumatol Surg Res.* 105. 1487-1493. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: SR and META (4 trials) Databases: Medline.</p> <p>Search period: 12 September 2018 and repeated on the 30th of September 2018.</p> <p>Inclusion Criteria: Randomised controlled clinical trials published in the English language. The study must have evaluated the efficacy of pre-operative gabapentin for pain relief in patients undergoing shoulder arthroscopy.</p> <p>Exclusion Criteria: Abstracts, comments, review articles and technique articles excluded.</p>	<p>Population: Any shoulder procedure performed through arthroscopic portals was included regardless of complexity.</p> <p>Intervention: Any pre-operative regimen of gabapentin administration was acceptable providing dosing was clearly defined in study methodology and the study included a control group that had been randomized to receive pre-operative placebo treatment.</p> <p>Comparison: Placebo.</p>	<p>Primary: Pain scores in the early postoperative period or reduction in post-operative opioid consumption (The consumption of post-operative opioids could not be pooled due to heterogeneity in reporting different medications).</p> <p>Secondary: Secondary outcomes included the incidence of nausea and vomiting within 24 hours of surgery and post-operative side effects, including dizziness and sedation.</p> <p>Results: Four randomised controlled trials were identified for inclusion (n = 227).</p> <p>Pain score: Pooled data analysis did not demonstrate a significant beneficial effect of using gabapentin for postoperative pain control (p = 0.12).</p> <p>Nausea and vomiting: Meta-analysis of pooled data from 4 studies revealed a significant beneficial effect of gabapentin in preventing nausea and vomiting in the postoperative period (OR 0.3, 95% CI 0.09, 0.92), as shown, with an unimportant heterogeneity between studies.</p> <p>One study demonstrated a significant reduction in opioid consumption after gabapentin. However, a significant difference was reported for postoperative dizziness or sedation in the gabapentin group.</p> <p>Author's Conclusion: Gabapentin is associated with significant reductions in post-operative pain, nausea and vomiting after shoulder arthroscopy. However, it does not appear to have an advantage with respect to post-operative pain control over other multimodal management strategies.</p>

**Methodical Notes**

Funding Sources: None.

COI: Professor Adnan Saithna and Dr Matt Daggett are consultants with Arthrex. The other authors declare that they have no conflict of interest.

Study Quality: Potential bias of studies was evaluated using the Cochrane Collaboration's tool. The majority of studies were deemed to have a low risk for the majority of bias categories.

Heterogeneity: Heterogeneity was measured and expressed as I<sup>2</sup>. Heterogeneity was low.

Publication Bias: n.a.

Notes: CEBM Level of Evidence (Oxford). EL 1 (Systematic review of randomized controlled trials)

- Notes:
- only one database searched, the number of included studies and participants is low
  - In two studies all patients received interscalene blocks (ISB) whilst in the other two studies ISB were not utilised (the authors did not report on the outcomes).
  - The dosages and administration time of gabapentin were inconsistent (300 mg - 800 mg)

Viscusi, E. R. et al. The Efficacy and Safety of the Fentanyl Iontophoretic Transdermal System (IONSYS((R))) in the Geriatric Population: A Randomized Controlled Trial

Meta-Analysis of Phase III and IIIb Trials. *Drugs Aging*. 33. 901-912. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 5</p> <p>Study type: Systematic review and meta-analysis (7 studies)</p> <p>To evaluate whether the efficacy and safety profile of fentanyl iontophoretic transdermal system (ITS) (IONSYS) was similar in geriatric (&gt;=65 years) and non-geriatric (&lt;65 years) patients.</p> <p>Databases: PubMed and the Cochrane Library, ClinicalTrials.gov</p> <p>Search period: 1980 to 30/06/2016</p> <p>Inclusion Criteria: Studies were included if they evaluated the fentanyl ITS in prospective, randomized controlled trials.</p> <p>Exclusion Criteria: not described.</p>	<p>Population: Not specified, but including geriatric patients as well as adults.</p> <p>Intervention: Fentanyl Iontophoretic Transdermal System (ITS group) (IONSYS)</p> <p>Comparison: Not specified in inclusion criteria, placebo or morphine IV according to table 2.</p>	<p>Primary: The treatment success rate, determined as a rating of 'excellent' or 'good' PGA of the method of pain control</p> <p>Secondary: Safety</p> <p>Results: Results: only summary results displayed here due to length, rest see article A total of 1763 patients were assigned to the fentanyl ITS treatment group. Of the 1763 patients, 499 patients were ≥65 years of age; 65.1% were 65–74 years of age, and 3.2% were ≥85 years of age. In the fentanyl ITS treatment group, there were no statistically significant differences between the non-geriatric and geriatric patients reporting success on the PGA at 24 h (80.0 vs. 83.0%, respectively; p = 0.001). There were no statistically significant differences between the groups in success rates on discharge (82.8 vs. 87.5%, respectively; p = 0.1195). The safety profile was similar between the groups.</p> <p>Author's Conclusion: The results of this analysis suggest that there were no mean differences in terms of efficacy in each of the geriatric age groups compared with the non-geriatric patients. Additionally, the safety profile of fentanyl ITS was fairly similar in the geriatric patients compared with non-geriatric patients. These results suggest that fentanyl ITS may be a valuable addition to the treatment of postoperative pain in geriatric patients.</p>

Methodical Notes

**Funding Sources:** The analyses and writing of this manuscript were supported financially by The Medicines Company.

**COI:** Eugene R. Viscusi is Professor of Anesthesiology and Director, Acute Pain Management at Thomas Jefferson University. He declares the following potential conflicts of interest: funded research to his institution—AcelRx and Pacira; consulting—AcelRx, Mallinckrodt, Cubist, Trevena, and Pacira; speaking honoraria—AstraZeneca, Mallinckrodt, Cubist, Salix, and Pacira. Li Ding and The Medicines Company (Parsippany, NJ, USA).

**Study Quality:** Risk of bias was assessed, but the tool was not described (likely Cochrane risk of bias), and no individual results were reported. Overall low risk of bias, while blinding was unclear in some studies.

**Heterogeneity:** Heterogeneity not investigated.

**Publication Bias:** Publication bias not investigated.

**Notes:**  
Oxford level of evidence: 1 Systematic review and meta-analysis.  
Recommend exclusion. due to poor quality.  
Unclear description of inclusion criteria. Heterogeneity and publication bias not investigated. Unclear if two investigators selected studies for inclusion.

Wang, J. et al. Impact of Ketamine on Pain Management in Cesarean Section: A Systematic Review and Meta-Analysis 2020

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (20 trials)</p> <p>The present meta-analysis aimed to evaluate the clinical efficacy of ketamine versus control in cesarean section anesthesia for reducing postoperative pain and analgesia</p> <p>Databases: Pubmed, Embase, Cochrane Library</p> <p>Search period: Inception to August 2018</p> <p>Inclusion Criteria: Study type: clinical RCTs using ketamine versus control in pain management for patients who underwent cesarean section were included. Patients: those who underwent cesarean section and fulfilled the following</p>	<p>Population: Those who underwent cesarean section and fulfilled the following criteria, such as American Society of Anesthesiologists grade I-II, elective full-term maternal, no major life events before birth, no severe pathological obstetrics, no severe complications such as hyperthyroidism, hypertension, and no history of mental illness,</p>	<p>Primary: Pain relief, the time point of first request of analgesics, and analgesic consumption</p> <p>Secondary:</p> <p>Results: Results: Due to length of the article, only summary results were displayed here. For further information see full text article</p> <p>A total of 20 RCTs with 1,737 patients who underwent cesarean section were included. Meta-analysis showed that the pain intensity in the ketamine group was less than that in the control group (mean difference [MD] -0.28, 95% CI -0.41 to -0.15, p &lt; 0.001).</p>

<p>criteria, such as American Society of Anesthesiologists grade I-II, elective full-term maternal, no major life events before birth, no severe pathological obstetrics, no severe complications such as hyperthyroidism, hypertension, and no history of mental illness, brain disease, drug abuse, or allergy. Interventions: in the experimental group, ketamine was administered intravenously or intraspinally for spinal anesthesia during cesarean section. Saline solution or other anesthetic agents were used as control similar to that of anesthesia. Outcomes: pain relief, the time point for the first request of analgesics, and morphine consumption</p> <p>Exclusion Criteria: Replications, reviews, animal experiments, studies with insufficient data, or high-risk bias were excluded.</p>	<p>brain disease, drug abuse, or allergy.</p> <p>Intervention: Ketamine was administered intravenously or intraspinally for spinal anesthesia during cesarean section.</p> <p>Comparison: Saline solution or other anesthetic agents were used as control similar to that of anesthesia.</p>	<p>95% confidence interval [CI], -1.61, &lt;0.0001). Application of ketamine cesarean section also resulted in d consumption of morphine when c with the control group (MD, -6.11 CI, -9.93, -2.29; P = 0.002). In add first time required for analge: significantly longer in the ketamin than that of the control group (M minutes; 95% CI, 50.85, 94.11; P &lt; 0.0</p> <p>Author's Conclusion: I supplementation during cesarean reduces pain and morphine consumption and prolongs the post analgesia.</p>
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**Methodical Notes**

**Funding Sources:** None.

**COI:** None.

**Study Quality:** The risk of bias was assessed according to the Cochrane Handbook based on the 7 aspects: random assignment, concealment, study blind method, outcome measure blindness, the integrity of the resulting, selective reporting, and other s evaluated based on "low bias," "unclear bias," and "high biased."

**Heterogeneity:** The chi-square test was used to detect the heterogeneity of the included studies. If  $P > 0.1$  and  $I^2 < 50\%$ , hom included studies and the fixed effect model was used for meta-analysis. If significant heterogeneity was detected betwe heterogeneity was analyzed, and the random-effects model was applied for the overall analysis.

**Publication Bias:** Moreover, publication bias analysis, Begg's test, Egger's test, and the funnel plot were used to present the res of Begg's test ( $P = 0.047$ ) and Egger's test ( $P = 0.044$ ) indicated a significant publication bias (Fig. 10).

**Notes:**  
Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (20 trials, 1,737 patients)  
Large number of trials and patients included.  
High heterogeneity was present for the main outcomes ( $I^2$  95%) which limits the implications of the article.  
Publication bias was present for the main outcomes, therefore the results should be interpreted with caution.

Wang, L. et al. The efficacy of gabapentin in reducing pain intensity and postoperative nausea and vomiting following la A meta-analysis. *Medicine (Baltimore)*. 96. e8007. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (9 trials)  The purpose of the current meta-analysis was to determine whether preoperative treatment with gabapentin is associated with lower pain scores, total morphine consumption, and postoperative nausea and vomiting (PONV) following laparoscopic cholecystectomy.</p> <p>Databases: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Google database, the Chinese Wanfang database, and the China National Knowledge Infrastructure (CNKI).</p> <p>Search period: Inception to March 2017</p> <p>Inclusion Criteria: Study type: clinical RCTs; Participants: patients prepared for laparoscopic cholecystectomy (ASA 3 and 4); Intervention: the experimental group received preoperative oral gabapentin, while the control group received a placebo or blank control. Outcomes: visual analog score (VAS) at 12 and 24 hours, total morphine consumption, and the occurrence of PONV.</p> <p>Exclusion Criteria: Comparison with other</p>	<p>Population: Patients prepared for laparoscopic cholecystectomy (ASA 3 and 4);</p> <p>Intervention: Preoperative oral gabapentin</p> <p>Comparison: Placebo or blank control</p>	<p>Primary: Visual analog scale (VAS) at 12 and 24 hours consumption, and the occurrence of PONV</p> <p>Secondary:</p> <p>Results: <u>Results:</u> Due to length, only summary results were For further information see full text article.</p> <p>A total of 9 studies involving 966 patients were identified. In 484 gabapentin subjects and 482 controls. Compared with th gabapentin was associated with lower VAS at 12 hours (WMD -17.36 to -2.80, <math>P=0.007</math>) and 24 hours (WMD=-6.33, 95% C <math>P=0.000</math>), which was equivalent on a 110-point VAS scale to 1 hours and 6.33 points at 24 hours. Compared with the gabapentin was associated with less total morphine approximately 110.83mg (WMD=-110.83, 95% CI: -183.25 to - addition, the occurrence of nausea and vomiting in gabapent (25.2% vs 47.6, <math>RR=0.53</math>, 95% CI: 0.44-0.63, <math>P=0.000</math>).</p> <p>Author's Conclusion: In conclusion, immediate analgesic eff sparing effects (PONV) were obtained with the administratic Additionally, the analgesic efficacy and opioid-sparing effects the high-dosage gabapentin group. Thus, we recomm administration high dose of gabapentin in reducing a laparoscopic cholecystectomy. Because the sample size an included studies were limited, a multicenter RCT is need optimal dose and timing of gabapentin in reducing a laparoscopic cholecystectomy.</p>

drugs (glucocorticoid or pregabalin);  
 Noninclusion of gabapentin drugs;  
 NonRCTs; Comments, reviews or with no  
 relevant outcomes

**Methodical Notes**

**Funding Sources:** Not described.

**COI:** None.

**Study Quality:** The quality of all included trials was independently assessed by 2 reviewers (LW and YD) on the basis of the Cochrane Reviews of Interventions, version 5.1.0 ([http:// handbook.cochrane.org/](http://handbook.cochrane.org/)). The Jadad score was used to quantitatively evaluate the quality of the studies. The Jadad scores were 2 in 3 studies, 3 in 2 studies, and 5 in 4 studies. The quality of all of the studies were acceptable. The quality ranged from 65.3% to 72.9%. The power of the meta-analysis of the total studies was 86.4%.

**Heterogeneity:** The heterogeneity between the studies was assessed using the I<sup>2</sup> test; if I<sup>2</sup> was less than or equal to 50%, then a fixed-effect model (Mantel–Haenszel) was applied to the data. We used a random effects model if I<sup>2</sup> was more than 50%. Substantial heterogeneity between the studies for the main outcomes: VAS at 12 hours (I<sup>2</sup>=95%) and Total morphine consumption at 24 hours (I<sup>2</sup>=55.7%). Heterogeneity was present for VAS at 24 hours (I<sup>2</sup>=55.7%).

**Publication Bias:** We then tested the publication bias using the funnel plot and Begg test; the results are shown in Figs. 5 and 6. No publication bias was found to be symmetrical, and Begg value was 0.952.

**Notes:**

**Oxford Level of Evidence:** 1 Systematic Review and Meta-Analysis of RCTs (9 trials)

Substantial heterogeneity between the studies for the main outcomes: VAS at 12 hours (I<sup>2</sup>=95%) and Total morphine consumption at 24 hours (I<sup>2</sup>=55.7%). This limits the implications of the article.

Overall the quality of the included studies was considered to be moderate by the authors.

Publication bias was not present.

**Wang, X. et al. Effect of Intravenous Dexmedetomidine During General Anesthesia on Acute Postoperative Pain in Adults: A Meta-Analysis of Randomized Controlled Trials. Clin J Pain. 34. 1180-1191. 2018**

Evidence level/Study Types	P - I - C	Outcomes/Results
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> Systematic Review and Meta-Analysis of RCTs (40 trials),            Thus, we conducted this systematic review and meta-analysis of randomized controlled trials DEX during general anesthesia for the treatment of acute postoperative pain.  <b>Databases:</b> PubMed, Embase, and Cochrane Central</p> <p><b>Search period:</b> Inception to April 2016</p> <p><b>Inclusion Criteria:</b> (1) designed as RCTs; (2) operation of all medical specialties were allowed; (3) comparison of DEX with placebo or other analgesic medications that were used during general anesthesia; (4) presenting acute pain-related outcomes within 24 hours postsurgery, which might be displayed as scores of pain scales, pain intensity, consumption of opioids, number of patients with moderate-to-high scores, or the number of patients requiring rescue analgesia</p> <p><b>Exclusion Criteria:</b> The nonrandomized studies, which performed with only nongeneral anesthesia (eg, spinal, neuraxial, or local anesthesia), using DEX by nonintravenous route (intramuscular, intrathecal, intraarticular), and evaluating the pain that exceeded 24 hours postsurgery.</p>	<p><b>Population:</b>            Patients undergoing surgery</p> <p><b>Intervention:</b>            DEX</p> <p><b>Comparison:</b>            Placebo or other analgesic medications that were used during general anesthesia;</p>	<p><b>Primary:</b> Acute pain-related outcomes within 24 hours postoperative pain might be displayed as scores of pain scales, pain intensity, consumption of opioids, number of patients with moderate-to-high scores, or the number of patients requiring rescue analgesia</p> <p><b>Secondary:</b></p> <p><b>Results:</b> <u>Results:</u> Due to length only summary results are provided. Compared with the normal saline group, patients using DEX significantly decreased pain intensity within 6 hours [WMD = -1.34; 95% CI, -1.34 to -0.53] and at 24 hours [WMD = -0.47; 95% CI, -0.83 to -0.11]. DEX usage significantly decreased cumulative opioids consumption at 24 hours after surgery [WMD = -10.16; 95% CI, -10.16 to -3.35], decreased the rescue opioid consumption in the postanesthesia care unit (WMD = -3.11; 95% CI, -5.20 to -1.02), and the risk of rescue analgesics (relative risk=0.49; 95% CI, 0.27-0.83). The interval to first rescue analgesia was prolonged (WMD = 20.27-49.59).</p> <p><b>Author's Conclusion:</b> Intravenous DEX effectively reduced pain intensity, extended the pain-free period, and decreased the consumption of opioids during postoperative recovery of adults in general anesthesia.</p>

**Methodical Notes**

**Funding Sources:** Supported by the Shandong Academy of Medical Sciences Foundation of China, Shandong, China (2015-3 Health Science Technology Development Foundation of China, Shandong, China (2015WS0153).

**COI:** None.

**Study Quality:** The quality of included trials was assessed by the Cochrane's risk of bias, which is based on 5 domains including randomization bias, detection bias, attrition bias, and reporting bias. All eligible studies showed satisfied quality.

Heterogeneity: The Cochran Q test and I2 test assessed the heterogeneity. P-value <0.05 was regarded as statistically significant heterogeneity, 25% to 75% was considered medium heterogeneity, and ≥75% was considered high heterogeneity. Pain intensity within 6 hours after surgery (I2=87.6%), pain scales at 24 hours postoperatively (I2=74.2%), opioids consumption=74.2%),

Publication Bias: Publication bias was examined by the funnel plot, Egger test, and Begg test. Pain intensity within 6 hours after surgery (I2=87.6%), pain scales at 24 hours postoperatively (I2=74.2%), opioids consumption=74.2%),

**Notes:**

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (40 trials)

Analysis is based on a large amount of included studies

All eligible studies showed satisfied quality.

Medium to high heterogeneity was present for the main outcomes which limits the implications for practice.

Publication bias was approximately not present.

Wang, Y. M. et al. Pregabalin can decrease acute pain and postoperative nausea and vomiting in hysterectomy (Baltimore). 96. e7714. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (10 trials, 1207 patients) To determine the efficacy and safety of the preoperative use of pregabalin to treat acute postoperative pain following hysterectomy. Databases: Pubmed, Embase, Web of Science, Cochrane Library and Google databases</p> <p>Search period: Inception to April 2017</p> <p>Inclusion Criteria: Patients: adults (age&gt;18 years) undergoing hysterectomy (abdominal hysterectomy; posthysterectomy and vaginal hysterectomy); Intervention: perioperative pregabalin as an intervention group; Comparison: placebo; Outcomes: visual analog scale (VAS) with rest or mobilization at 2, 4, and 24 hours, total morphine consumption at 2, 4, 24, and 48 hours and complications (nausea, vomiting, sedation and dizziness); Study design: RCTs.</p> <p>Exclusion Criteria: We excluded patients undergoing laparoscopic hysterectomy because the pain intensity of this surgery was much lower than that of abdominal hysterectomy.</p>	<p>Population: Adults (age&gt;18 years) undergoing hysterectomy (abdominal hysterectomy; posthysterectomy and vaginal hysterectomy)</p> <p>Intervention: Perioperative pregabalin</p> <p>Comparison: Placebo</p>	<p>Primary: Visual analog scale (VAS) with rest or mobilization at 2, 4, 24, and 48 hours, total morphine consumption at 2, 4, 24, and 48 hours, and complications (nausea, vomiting, sedation and dizziness)</p> <p>Secondary:</p> <p>Results: <u>Results:</u> Due to length, only summary results were here. Ten clinical studies with 1207 patients (pregabalin=760, placebo=447) were finally included in this meta-analysis. Preoperative administration of pregabalin was associated with a significant reduction in total morphine consumption at 2, 4, 24, and 48 hours after hysterectomy. The occurrence of morphine-related complications (nausea and vomiting) was also reduced in the pregabalin group. However, the preoperative administration of pregabalin was associated with an increase in the occurrence of dizziness. There was no significant difference in the occurrence of sedation.</p> <p>Author's Conclusion: The preoperative use of pregabalin can reduce postoperative pain, total morphine consumption, and morphine-related complications following hysterectomy. The doses of pregabalin were different, and large heterogeneity was the limitation of the meta-analysis. Further studies should determine the optimal dose of pregabalin for controlling acute pain after hysterectomy.</p>

**Methodical Notes**

Funding Sources: Not stated.

COI: None.

Study Quality: The methodological quality of all included trials was independently assessed by 2 reviewers using the Cochrane Risk of Bias tool, version 5.1.0

The risk of bias of random sequence generation showed an unclear risk of bias in 2 studies. The risk of bias of allocation concealment showed an unclear risk of bias in 2 studies. The risk of bias of blinding of participants and personnel showed an unclear risk of bias in 2 studies. The risk of bias of blinding of outcome assessment showed an unclear risk of bias in 3 studies. The risk of bias of other bias showed an unclear risk of bias in one study. The risk of bias of sample calculation method showed an unclear risk of bias in one study.

Heterogeneity: Statistical heterogeneity was tested using the Chi-squared test and I2 statistic. When there was no statistical evidence of heterogeneity, a fixed-effects model was adopted; otherwise, a random-effect model was chosen. Substantial heterogeneity was present for the outcomes of pain intensity at 24 hours, occurrence of vomiting, occurrence of sedation.

Publication Bias: Publication bias was tested using funnel plots. Publication bias was assessed by funnel plot and quantitative assessment of publication bias of VAS with rest at 2, 4, and 24 hours and VAS with mobilization at 2, 4, and 24 hours were assessed by funnel plot. The results indicated that there was no publication bias among the included studies

**Notes:**

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (10 trials, 1207 patients)

Overall the quality of the included studies was rated as high by the authors.

Substantial heterogeneity was present for the main outcomes except VAS with mobilization at 24 hours, occurrence of vomiting.



Therefore the impact of this article for practice is limited.  
Publication bias was not present.

Xu, B. et al. Analgesic efficacy and safety of ketamine after total knee or hip arthroplasty: a meta-analysis of randomised  
BMJ Open. 9. e028337. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (10 trials)</p> <p>Databases: Pubmed, Embase, Cochrane Library</p> <p>Search period: Inception to 22 May 2019</p> <p>Inclusion Criteria: Randomised controlled trials comparing the efficacy and safety of ketamine with placebo for postoperative pain relief in patients undergoing total knee or hip arthroplasty.</p> <p>Exclusion Criteria: (1) <i>in vitro</i> studies, animal studies, reviews, letters and case reports; (2) experimental or control group received additional treatments; (3) data not available for extraction and (4) unavailability of the full text.</p>	<p>Population: Patients undergoing total knee or hip arthroplasty surgery;</p> <p>Intervention: Administration of ketamine for postoperative pain relief</p> <p>Comparison: Administration of saline in the control group</p>	<p>Primary: Pain intensity (0–8-hour, and 8–24-hour postoperative)</p> <p>Secondary: Cumulative morphine consumption (0–24-hour and 0–48-hour postoperative) and adverse effects</p> <p>Results: A total of 10 studies were included. One of them was rated as low quality. Intravenous placebo, intravenous ketamine was effective for pain relief during 0–8-hour (WMD -1.21, 95%CI -1.45 to -0.98, p&lt;0.001; three studies, 149 participants) and 8–24-hour postoperative periods, and effective for reduction of cumulative morphine consumption during both 0–24-hour (WMD -17.76, 95%CI -31.25 to -4.27, p=0.01; five studies, 303 participants) and 0–48-hour (WMD -21.79, 95%CI -25.46 to -18.11, p&lt;0.001; four studies, 255 participants) postoperative periods, without increasing risks of gastrointestinal or psychotic adverse effects. Limited data available for intra-articular (WMD -0.49, 95%CI -0.70 to -0.29, p&lt;0.001; 1 study, 18 participants) and epidural (WMD -2.10, 95%CI -3.30 to -0.90, p&lt;0.001; 1 study, 18 participants) ketamine pointed to a significant reduction in pain intensity during 8–24-hour postoperative periods. The analysis of pooled data revealed that the incidence of adverse effects in the administration of ketamine group was significantly lower than that in the control group for gastrointestinal adverse effects (RR 0.67, 95%CI 0.51 to 0.89, p=0.005; four studies, 303 participants) but not to psychotic adverse effects (RR 0.94; 95%CI 0.59 to 1.50; p=0.79; three studies, 18 participants). The combined data of two studies (17/18) showed that there were no differences between the intra-articular administration of ketamine group and control group with regard to gastrointestinal adverse effects (RR 1.00, 95%CI 0.53 to 1.89, p=0.99; 1 study, 18 participants), with no substantial heterogeneity (I<sup>2</sup> =0%; p=0.51). In addition, one study (18 participants) showed that there was no significant difference between the intra-articular administration of ketamine and the control group with regard to psychotic adverse effects (RR 1.05, 95%CI 0.36 to 3.11, p=0.94; one study, 39 participants).</p> <p>Author's Conclusion: Intravenous administration of ketamine is effective and safe for pain relief in patients undergoing total knee or hip arthroplasty. Nevertheless, the analgesic efficacy and safety of ketamine in such patients seem to vary by different administration routes. Further studies to explore</p>

#### Methodical Notes

**Funding Sources:** This work was supported by the Innovation Foundation of the Central South University for Postgraduate (2016Q03), the National Natural Science Foundation of China (81772413, 81472130, 81672225, 81601941, 81501923, 81702207 and 81702206), the Science and Technology Office of Hunan Province (2017TP1005), the Key Research and Development Program of Hunan Province (2017TP1005), the Investigator Grant of Xiangya Hospital, Central South University (2016Q03 and 2016Q06), the Xiangya Clinical Big Data System (2016Q06), the Clinical Scientific Research Foundation of Xiangya Hospital, Central South University (2015L03), the Project of Central South University (182130) and the Natural Science Foundation of Hunan Province (2017JJ3491, 2017JJ3492 and 2018JJ2001).

**COI:** None.

**Study Quality:** The Cochrane Collaboration's recommended tool was used to assess the methodological quality of included studies. The quality of included studies was considered to be high by the authors. Only one study was rated as low quality. High risk of bias due to other factors was present in seven studies.

**Heterogeneity:** The homogeneity of the effect size across trials was tested by the Q statistic (p<0.05 was considered heterogeneous). In the presence of heterogeneity among the studies, the random-effects model was used; otherwise, the fixed-effects model was considered acceptable. The I<sup>2</sup> statistic, which measures the proportion of the total variation across studies as a result of heterogeneity expressed as a percentage, was also used.

Substantial heterogeneity was observed for pain intensity during the late (I<sup>2</sup> =90%; p<0.001), but not the early (I<sup>2</sup> =50%, p=0.14) postoperative periods. An analysis was conducted to explore the potential sources of heterogeneity, but the exclusion of any single study did not change substantially. Substantial heterogeneity was observed for cumulative morphine consumption during the late (I<sup>2</sup> =90%; p<0.001), but not the early (I<sup>2</sup> =50%, p=0.14) postoperative periods.

**Publication Bias:** Begg's tests and funnel plots were performed to assess publication bias.

Funnel plots did not reveal any substantial asymmetry, and Begg's rank correlation test did not indicate publication bias among the included studies for the main outcomes pain intensity and cumulative morphine consumption.

#### Notes:

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (10 trials)

The overall quality of the included studies was considered to be high by the authors. Only one study was rated as low quality.

Publication bias was not present for the main outcomes.  
 Substantial heterogeneity was observed in part of the results (pain intensity during the late period, cumulative morphine consumption).  
 Therefore the implication for practice may be limited.  
 The results for pain intensity are based on only 3 or 6 studies, for cumulative morphine consumption only 5 or 4 studies

Ye, F. et al. Effect of intravenous ketamine for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. *Journal of Clinical Pharmacy and Therapeutics* (Baltimore). 96. e9147. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (5 trials, 212 patients)</p> <p>To assess the efficacy and safety of ketamine for reducing pain and narcotic use for patients undergoing LC</p> <p>Databases: Medline, Pubmed, Embase, ScienceDirect, Web of Science</p> <p>Search period: Inception to 2017</p> <p>Inclusion Criteria: Participants: Patients suffering symptomatic gallstones or cholecystitis and prepared for LC were included in our study; Interventions: Intravenous ketamine; Comparisons: Placebo; Outcomes: Postoperative pain measured by visual analog scale (VAS), narcotic use, and postoperative complications (nausea, vomiting, ileus, and pruritus); and Study design: Randomized controlled trials were eligible for inclusion.</p> <p>Exclusion Criteria: Exclusion criteria included articles would be excluded from the present meta-analysis for case reports, conference abstract, or review articles.</p>	<p>Population: Patients suffering symptomatic gallstones or cholecystitis and prepared for LC</p> <p>Intervention: Intravenous ketamine</p> <p>Comparison: Placebo</p>	<p>Primary: Postoperative pain measured by visual analog scale (VAS), postoperative complications (nausea, vomiting, ileus, and pruritus)</p> <p>Secondary:</p> <p>Results: <u>Results:</u> Five studies were included, with a total sample size of 212 patients. Current meta-analysis revealed that there were significant differences in postoperative pain score at 12 hours [standard mean difference (SMD)=-0.594, 95% CI: -0.594 to -0.050, P=.020], 24 hours (SMD)=-0.605 to -0.059, P=.017), and 48 hours (SMD=-0.340, 95% CI: -0.612 to -0.066, P=.002). Ketamine intervention was found to significantly decrease narcotic use at 12 hours (SMD=-0.296, 95% CI: -0.567 to -0.025, P=.033), 24 hours (SMD=-0.310, 95% CI: -0.609 to -0.011, P=.002), and 48 hours (SMD=-0.338, 95% CI: -0.609 to -0.066, P=.002). A significant difference in the incidence of nausea was found between the 2 groups (RD=-0.291 to -0.036, P=.012). The pooled results demonstrated that there was no significant difference in the incidence of pruritus in control groups (RD=-0.119, 95% CI: -0.218 to -0.020, P=.002), and a significant difference regarding the incidence of ileus (RD=-0.091, 95% CI: -0.182 to -0.001, P=.038).</p> <p>Author's Conclusion: Ketamine appeared to significantly reduce postoperative narcotic use following LC. On the basis of the current evidence available, RCTs are still required for further research.</p>

**Methodical Notes**

Funding Sources: Not described.

COI: None.

Study Quality: Quality assessment of the included RCTs is assessed by 2 authors independently according to the Cochrane Handbook of Interventions 5.0.  
 Evidence quality for each outcome was low.

Heterogeneity: The Chi-squared test and I<sup>2</sup> statistic are used to test for the presence of statistical heterogeneity. P50% at heterogeneity and a random-effects model is adopted. A fixed-effects model is applied when no significant heterogeneity is found. No heterogeneity was present in the different analyses (I<sup>2</sup>=0% for the main outcomes)

Publication Bias: Funnel plot was used to assess the publication bias of the main outcomes. The funnel plot diagrams of postoperative pain at 12 hours are symmetrical, indicating a low risk of publication bias

Notes:  
 Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis of RCTs (5 trials, 212 patients)  
 Analysis is based on only 5 RCTs including 212 patients. This may lead to an overestimation of the treatment effect.  
 Evidence quality for each outcome was low. This may influence the results of the meta-analysis.  
 No heterogeneity was present in the analysis (I<sup>2</sup>=0% for the main outcomes)

Zhong, W. G. et al. Dexmedetomidine for antiemesis in gynecologic surgery: a meta-analysis of randomized controlled trials. *Journal of Clinical Pharmacy and Therapeutics* (Baltimore). 14566-76. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results
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<p>Evidence level: 1</p> <p>Study type: Systematic Review and Meta-Analysis of RCTs (11 trials, 692 patients)</p> <p>This meta-analysis was conducted to evaluate the efficacy of dexmedetomidine on PONV after gynecological surgeries.</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL), Embase and PubMed</p> <p>Search period: Inception to 2015</p> <p>Inclusion Criteria: (1) trial: randomized controlled trials (RCTs); (2) patients: adults underwent gynecologic surgery; (3) interventions: dexmedetomidine versus placebo; (4) outcome: postoperative nausea or vomiting.</p> <p>Exclusion Criteria: (1) trial: non-randomized controlled trials (NRCTs), animal experiments, review articles; (2) patients: children or underwent other surgeries; (3) interventions: agent/combinational agents (including dexmedetomidine) versus agent/combinational agents; (4) outcome: relevant data could not be obtained from the original author. (5) duplications or abstracts only.</p>	<p>Population: Adults underwent gynecologic surgery</p> <p>Intervention: Dexmedetomidine</p> <p>Comparison: Placebo</p>	<p>Primary: Postoperative nausea or vomiting.</p> <p>Secondary: Side effects: Cardiovascular complications, Shiv Headache</p> <p>Results: Results: Due to length only summary results are disp further information see full text article.</p> <p>Eleven RCTs with 692 patients were included in this Dexmedetomidine a bridged postoperative nausea [Risk Ratio confidence interval (CI): 0.44 to 0.79] and vomiting [RR=0.48, 95% CI 0.06-0.64] compared with placebo. Despite of higher incidence of bradycardia [RR 2.87, 95% CI 1.08 to 7.58] and hypotension [RR 1.43 to 12.69], we found significant decrease in postoperative nausea [RR 0.23, 95% CI 0.13 to 0.40] and pruritus [RR 0.40, 95% CI 0.13 to 0.64] compared with placebo. Significant reductions in intraoperative fentanyl (RR 0.10, 95% CI 0.01-0.76, I<sup>2</sup> 0%), antiepileptic drugs (RR 0.39-0.99, I<sup>2</sup> 0%) and postoperative analgesic (RR 0.18, 95% CI 0.01-0.76, I<sup>2</sup> 0%) were also elicited.</p> <p>Author's Conclusion: The current meta-analysis exhibits that dexmedetomidine is superiority to placebo in attenuating the incidence of PONV, shivering, pruritus, as well as the pain scores in patients undergoing gynecological surgeries. Still, the potential cardiovascular complications should be taken seriously.</p>
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**Methodical Notes**

Funding Sources: Not stated.

COI: None.

Study Quality: Two authors (G.X.Y. and Z.M.) independently evaluated the quality of the included trials in accordance with the Cochrane Collaboration.

Overall the quality of the included studies was rated as high by the authors.

Heterogeneity: I<sup>2</sup> statistic was used to evaluate heterogeneity. I<sup>2</sup> ≤50% meant low risk heterogeneity, and a fixed-effect model or random-effect model would be employed.

Nausea (I<sup>2</sup>=5%), Vomiting (I<sup>2</sup>=0%), intraoperative bradycardia (I<sup>2</sup>=0%), hypotension (I<sup>2</sup>=0%), Shivering (I<sup>2</sup>=0%), Pruritus (I<sup>2</sup>=16%)

Publication Bias: Potential publication bias were evaluated by Egger's Test and Begg's Test

Notes:

Oxford Level of Evidence: 1 Systematic Review and Meta-Analysis (11 trials, 692 patients)

Overall the quality of the included studies was rated as high by the authors.

No heterogeneity for the main outcomes.

Publication bias was not present.

The number of the included trials for vomiting and side effects was small, this may lead to an overestimation of the effect sizes for these outcomes.

**Zou, Z. et al. Single dose intra-articular morphine for pain control after knee arthroscopy. Cochrane Database Syst Rev.**

Evidence level/Study Types	P - I - C	Outcomes/Results
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (28 studies)</p> <p>To evaluate the relative effects on pain relief and adverse events of IA morphine given for pain control after knee arthroscopy compared with</p>	<p>Population: We included participants of either gender, aged 15 years or older, and undergoing knee arthroscopy.</p> <p>Intervention: Single dose IA morphine for the</p>	<p>Primary: 1. Patient-reported postoperative pain intensity (a 0 - 10 cm VAS score). 2. Use of supplementary analgesic (number of participants using rescue analgesics, time to first rescue analgesics, analgesic drug counts, patient-controlled analgesia or consumption, etc.).</p> <p>Secondary: 1. Adverse events. 2. Withdrawals.</p> <p>Results: Results: only summary results displayed here, due to length, rest see article. We included 28 small, low quality studies (29 reports) involving 2564 participants. Only 21 studies (21 reports) comparing morphine with placebo, nine studies with adequate data were included in the meta-analysis. Overall, the risk of bias was unclear. Overall, the quality of evidence assessed using GRADE was low to very low, downgraded primarily due to risk of bias, small study size, and imprecision.</p> <p>No statistical difference was found between 1 mg IA morphine and placebo in pain inter</p>

placebo, other analgesics (local anaesthetics, non-steroidal anti-inflammatory drugs (NSAIDs), other opioids) and other routes of morphine administration.

Databases: CENTRAL, MEDLINE via Ovid, EMBASE, and the reference lists of included articles. We also searched the metaRegister of controlled trials, clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing trials.

Search period: Inception 05 / 2015

Inclusion Criteria: All the randomised, double-blind controlled trials that compared single dose IA morphine with other interventions for the treatment of postoperative pain after knee arthroscopy.

Exclusion Criteria: We excluded studies with fewer than 10 participants in each group, using spinal or epidural anaesthesia, or assessing the analgesic effect of IA morphine on chronic pain.

treatment of postoperative pain  
Comparison: other interventions for the treatment of postoperative pain

(visual analogue scale (VAS)) at early phase (zero to two hours) (mean difference (MD) -0.95, 95% CI -1.15 to 0.14; participants = 297; studies = 7; low quality evidence), medium phase (two to six hours) (MD -0.47, 95% CI -1.09 to 0.14; participants = 297; studies = 7; low quality evidence) and late phase (six to 30 hours) (MD -0.88, 95% CI -1.81 to 0.04; participants = 297; studies = 7; low quality evidence). No significant difference was found between 1 mg IA morphine for pain intensity at early phase (MD -0.56, 95% CI -1.93 to 0.81; participants = 105; studies = 2; low quality evidence), while 4 mg/5 mg morphine provided better analgesia than 1 mg morphine at late phase (MD 0.67, 95% CI 0.08 to 1.25; participants = 97; studies = 2; low quality evidence). IA morphine was not better than local anaesthetic agents at early phase (MD 1.43, 95% CI 0.49 to 2.37; participants = 248; studies = 5; low quality evidence), NSAID at early phase (MD 0.95, 95% CI -0.95 to 2.85; participants = 80; studies = 2; very low quality evidence), sufentanil, fentanyl or pethidine for pain intensity. IA morphine was similar to intramuscular (IM) morphine for pain intensity at early phase (MD 0.21, 95% CI -0.48 to 0.90; participants = 72; studies = 2; very low quality evidence).

Meta-analysis indicated that there was no difference between IA morphine and placebo or bupivacaine in time to first analgesic request. Eleven out of 20 studies comparing morphine with placebo reported adverse events and no statistical difference was obtained regarding the incidence of adverse events (risk ratio (RR) 1.09, 95% CI 0.51 to 2.36; participants = 297; studies = 8; low quality evidence). Seven of 28 studies reported participants' withdrawals. There were not enough data for withdrawals to be able to perform meta-analysis.

Author's Conclusion: Implications for practice This review did not find high quality evidence that 1 mg IA morphine is better than placebo at reducing pain intensity at early, medium and late phases. No statistical difference was reported between IA morphine and placebo regarding the incidence of adverse events. The relative effects of 1 mg morphine compared with IA bupivacaine, NSAIDs, sufentanil, fentanyl and pethidine are uncertain. The quality of the evidence is limited by high risk of bias and small size of the included studies, which might bias the results. More high quality studies are needed to get more conclusive results.

## Methodical Notes

### Funding Sources: Internal sources

- National Nature Science Foundation of China, China. [81000525](#)
- Shanghai Chen-guang program, China. 10CG40
- Shanghai Health Bureau, China. XYQ2011022

### External sources

- No sources of support supplied

COI: ZZ's and YYS's institution received funding support from the National Nature Science Foundation of China (81000525), (10CG40) and Shanghai Health Bureau (XYQ2011022), to complete this review.

Study Quality: Two authors assessed risk of bias for each study independently, based on the methods used to generate concealment, blinding, follow-up, selective reporting and group size according to the 'Risk of bias' tool. Overall quality of the body of evidence was assessed using GRADE summary of findings.

"Overall, the risk of bias was unclear. Overall, the quality of the evidence assessed using GRADE was low to very low, downgraded due to small study size, and imprecision."

Heterogeneity: We tested the heterogeneity between studies using the Chi<sup>2</sup> test (with P < 0.1 indicating significant heterogeneity). We described the proportion of variability due to heterogeneity (Higgins 2003). When P > 0.1, we carried out the meta-analysis using a random effects model.

We carried out subgroup analysis to assess clinical heterogeneity rather than statistical heterogeneity. We carried out separate analyses for clinical parameters as follows. Phases of postoperative pain, and comparisons.

Publication Bias: Publication bias considered in the GRADE summary of findings, but not investigated or reported using funnel plot.

**Notes:**

**Oxford level of evidence: 1 Systematic review and meta-analysis**

**Overall low or very low quality evidence.**

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**Schlüsselfrage:**

**3.3.2.2 Wundrandinfiltration**

Führt bei Erwachsenen (P) die intraop. Wundrandinfiltration/peritoneale Instil. (I) im Vergleich zu keiner Intervention (C) zu einer verbesserten Analgesiequalität (O: VAS/Morphinverbrauch/Opioid-induzierte Nebenwirkungen)? bzw. zu substanzspez. NW?

**Inhalt: 22 Literaturstellen**

Literaturstelle	Evidenzlevel	Studientyp
Adesope, O. 2016	2	Systematic review and meta-analysis (21 studies). The objective is to assess the efficacy of local anaesthetic wound infiltration in reducing pain scores and opioid consumption in women undergoing caesarean delivery.
Bai, J. W. 2020	2	Systematic review (89 studies). To determine the effectiveness of various adjunct agents for direct co-infiltration with LA into subcutaneous or muscular layers of surgical wounds.
Bamigboye, A. A. 2009	1	Systematic review and meta-analysis: (20 studies) To assess the effects of local anaesthetic agent wound infiltration/irrigation and/or abdominal nerve blocks on post-caesarean section pain and the mother's well being and interaction with her baby.
Boddy, A. P. 2006	2	Systematic Review and Meta-Analysis (16 studies) To evaluate the effects of intraperitoneal local analgesia on early postoperative abdominal pain after laparoscopic cholecystectomy.
Choi, G. J. 2015	1	Systematic review and meta-analysis (39 RCTs) To systematically evaluate the effect of intraperitoneal local anesthetic on pain characteristics after laparoscopic cholecystectomy (LC).
Hamill, J. K. 2017	1	Systematic review of systematic reviews. (9 included articles) To compare the efficacy of IPLA between different types of procedure and to formulate GRADE recommendations for the use of IPLA.
Hamilton, T. W. 2017	1	Systematic review (9 studies) To assess the analgesic efficacy and adverse effects of liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain.
Hong, S. S. 2018	1	Systematic review and meta-analysis To determine the effect of CLA infusion post cardiac surgery on pain, time to ambulation, severe adverse events, patient satisfaction, time to extubation, length of stay in the intensive care unit and in the hospital, total narcotic consumption, and pulmonary function.
Joshi, G. P. 2012	2	Systematic review and meta-analysis (79 studies) The aim of this systematic review was to evaluate the available literature on the management of pain after open hernia surgery.
Kahokehr, A. 2011	1	Systematic review and meta-analysis (5 studies) To investigate the clinical effects of intraperitoneal local anaesthetic (IPLA) in laparoscopic gastric procedures.
Kjaergaard, M. 2012	1	Systematic review (9 studies) To evaluate the effect of wound infiltration with local anesthetics on post-operative pain, supplemental analgesic consumption, time to first analgesic request, as well as on side effects in patients undergoing lumbar spine surgery by using evidence from all relevant double-blind, randomized and controlled trials.
Loizides, S. 2014	1	Systematic review and meta-analysis: 19 studies To assess the benefits and harms of local anaesthetic wound infiltration in patients undergoing laparoscopic cholecystectomy and to identify the best method of local anaesthetic wound infiltration with regards to the type of local anaesthetic, dosage, and time of administration of the local anaesthetic.
Marks, J. L. 2012	1	Systematic review and meta-analysis (7 studies) To review the effect of intraperitoneal instillation of local anesthetics at laparoscopy on postoperative pain after laparoscopic surgery performed to treat benign gynecologic conditions.
Marques, E. M. 2014	1	Systematic review and meta-analysis (13 studies). To synthesise evidence from randomised controlled trials (RCTs) evaluating the

		effectiveness of peri-operative local anaesthetic infiltration for pain control in patients with THR and TKR.
Mungroop, T. H. 2019	2	Systematic review and meta-analysis: (26 studies) To assess whether the location of wound catheters (ie, preperitoneal vs. subcutaneous) impacts outcomes, when compared with alternatives such as epidural analgesia.
Ren, Y. 2019	1	Systematic review and meta-analysis: 5 studies "To evaluate effects of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia in abdominal surgery."
Seanglelur, A. 2016	1	Systematic review and meta-analysis: 28 studies.
Tam, K. W. 2015	2	Systematic review and meta-analysis: 13 studies A systematic review of randomized controlled trials to evaluate the efficacy of bupivacaine or ropivacaine analgesia for pain relief in breast cancer surgery.
Tong, Y. S. 2014	1	Systematic review and meta-analysis (8 studies) To evaluate the efficacy of extraperitoneal bupivacaine treatment during laparoscopic inguinal hernia repair for the reduction of postoperative pain.
Ventham, N. T. 2014	1	Systematic review and meta-analysis (12 studies). This study aims to evaluate the efficacy of novel local anesthetic techniques in colorectal surgery.
Wang, J. 2016	2	Systematic review and meta-analysis (6 studies) To assess the safety and efficacy of local anesthetic infiltration around nephrostomy tract on postoperative pain control after percutaneous nephrolithotomy.
Yong, L. 2017	1	Systematic review and meta-analysis (12 studies). To assess the benefits and disadvantage of intraperitoneal instillation of ropivacaine in people undergoing laparoscopic cholecystectomy.

**OXFORD (2011) Appraisal Sheet: Systematic Reviews: 22 Bewertung(en)**

Adesope, O. et al. Local anaesthetic wound infiltration for postcaesarean section analgesia: A systematic review and meta-analysis. <i>Eur J Anaesthesiol.</i> 33. 731-42. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review and meta-analysis (21 studies). The objective is to assess the efficacy of local anaesthetic wound infiltration in reducing pain scores and opioid consumption in women undergoing caesarean delivery.</p> <p>Databases: MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled trials (CENTRAL)</p>	<p>Population: Caesarian section patients.</p> <p>Intervention: Infusion techniques for postcaesarean section analgesia.</p> <p>Comparison: Single wound infiltration with a local anaesthetic postcaesarean section analgesia.</p>	<p>Primary: Pain intensity scores and opioid consumption at 24 h.</p> <p>Secondary: Pain intensity scores at 6 and 48 h, opioid consumption at 6 and 48 h, duration of hospitalisation, side-effects, need for rescue analgesics and patient satisfaction.</p> <p>Results: Results: Only summary results displayed here, due to length: rest see full article. A total of 21 studies were included in the final analysis (11 studies using an infusion technique and 10 studies using single infiltration). Local anaesthetic wound infiltration significantly decreased opioid consumption at 24 h [mean difference -9.69mg morphine equivalents, 95% confidence interval (CI), -14.85 to -4.52] and pain scores after 24 h at rest (mean difference -0.36, 95% CI, -0.58 to -0.14) and on movement (mean difference -0.61, 95% CI, -1.19 to -0.03). Subgroup analysis did not suggest a difference in primary outcomes between infusions and single infiltration. Opioid consumption was reduced in patients who did not receive intrathecal morphine but not in those who received intrathecal morphine, although there were very little data in patients receiving intrathecal morphine. Pain scores at rest and on movement at 24 h were reduced with catheter placement below the fascia but not above the fascia. There were no statistically significant reductions in nausea, vomiting or pruritus with local anaesthetic infiltration.</p> <p>Author's Conclusion: In conclusion, this systematic review and meta-analysis suggests that local anaesthetic wound infiltration provides a postoperative opioid-sparing effect but was associated with only a small reduction in pain scores and no statistically significant reduction in opioid-related sideeffects. The value of this technique in patients receiving ITM remains less clear and should be investigated in future studies.</p>	<p>21 studies included: Bengsghir 2008, Carvalho 2010, Corsini 2013, Demiraran 2013, Ducarme 2012, Eldaba 2013, Fredman 2000, Givens 2002, Jabalameli 2012, Jolly 2015, Kainu 2012, Kessous 2012, Larsen 2015, Lavand'homme 2007, Mecklem 1995, Pavy 1994, Reinikainen 2014, Sekhavat 2011, Trotter 1991, Tuncer 2010, Zohar 2006.</p>

Search period:  
Inception -  
until  
December  
2015.

Inclusion  
Criteria:  
Randomised  
controlled  
trials that  
assessed the  
efficacy of  
infusion  
techniques or  
single wound  
infiltration  
with a local  
anaesthetic  
for  
postcaesarean  
section  
analgesia.

Exclusion  
Criteria:  
Abstracts,  
reviews,  
letters to the  
editors,  
retrospective  
studies and  
case reports  
were  
excluded.

#### Methodical Notes

Funding Sources: None.

COI: None.

**Study Quality:** The selected articles meeting the inclusion criteria were assessed separately by two reviewers using the risk of bias assessment tool suggested by the Cochrane Collaboration. The criteria evaluated were selection bias (randomisation, sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and selective reporting bias. Each study was assessed in each parameter as low, unclear or high risk of bias. Any discrepancies were resolved by discussion with the third reviewer (AH).  
Risk of bias was considered to be low in most cases.

**Heterogeneity:** A random effects model was used. We considered heterogeneity to be present if I<sup>2</sup> was greater than 50%. Forest plots were used to graphically present and evaluate treatment effects. Subgroups were compared using the Q-test.

**Publication Bias:** We assessed for publication bias for the primary outcomes using funnel plots and Egger's test. In case of an asymmetrical funnel plot and statistically significant Egger test, we assessed for missing studies using the trim and fill method<sup>14</sup> and examined the contour-enhanced funnel plots.

#### Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.

Downgrade to evidence level 2.

Unclear definition of controls. This is likely the cause for the high heterogeneity in most comparisons, which limits the implications from this article.

Bai, J. W. et al. Adjuncts to local anesthetic wound infiltration for postoperative analgesia: a systematic review. *Reg Anesth Pain Med.* 45. 645-655. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Systematic review (89 studies). To determine the effectiveness of various adjunct agents for direct co-	Population: Human adults in the perioperative setting  Intervention: Adjunct and LA agents were locally infiltrated	Primary: Reduction in postoperative opioid requirement.  Secondary: Time-to-first analgesic use, postoperative pain score, any reported adverse effects.  Results: Only summary results presented here, due to length, rest see article. "89 RCTs were identified, adjuncts included opioids, NSAIDs, steroids, alpha-2 agonists, ketamine, magnesium, neosaxitoxin,	89 studies included, see full article for list.



infiltration with LA into subcutaneous or muscular layers of surgical wounds.

Databases: Medline, Embase, CCTR, CDSR, SCopus, Web of Science, Clinicaltrials.gov

Search period: Inception - 01 / 2019

Inclusion Criteria:  
 (1) randomized controlled trials on human adults in the perioperative setting and  
 (2) adjunct and LA agents were locally infiltrated into the surgical wound or subcutaneous tissue for postoperative analgesia.

Exclusion Criteria:  
 (1) infiltration was outside the surgical setting or not used for surgical analgesia  
 (2) the LA or adjunct were used for an indication other than wound infiltration, such as regional, neuraxial or peripheral nerve block techniques  
 (3) the infiltrative technique was peri-articular or intra-articular, peritonsillar, intra-oral, or dental, topical, fascial plane block  
 (4) the adjunct was only epinephrine and  
 (5) neither postoperative pain nor analgesic consumption were assessed.

into the surgical wound or subcutaneous tissue for postoperative analgesia.

Comparison: placebo or control or LA with adjunct co-infiltration or adjunct administered systemically.

methylene blue.

Alpha 2 agonists have the most evidence to support their use as adjuncts to LA infiltration. Fentanyl, ketorolac, dexamethasone, magnesium and several others show potential as adjuncts but require more evidence. Most studies support the the safety of these agents. Our findings suggest benefits of several adjuncts to infiltrative anesthesia for postoperative analgesia."

Author's Conclusion: "In conclusion, this systematic review found that alpha-2 agonstis have sufficient evidence to support their use as adjuncts to LA infiltration, while fentanyl, ketorola, dexamethasone, magnesium and several other agents show potential but require more evidence. Generally, infiltraiton of these agents appears to be safe. More trails are needed to support the effectiveness and safety of these adjuncts, as current trials are limited by sample size and methodological rigor."

**Methodical Notes**

**Funding Sources:** The authors have not declared a specific grant for this research from any funding agency in the publica, commercial or nor-for profit sectors.

**COI:** Resarch grant from Fisher and Paykel, unrelated to topic. Previous honoraria from Philipps, also not relevant to topic.

**Study Quality:** Quality was assesed using the Jadad scale and Cochrane risk of bias tool by two reviewers.

**Heterogeneity:** Not applicable, no meta-analysis was performed.

**Publication Bias:** Not investigated.

**Notes:**

Oxford level of evidence 1: systematic review and meta-analysis.

Downgrade to evidence level 2.

Results and conclusion do not fully support the primary outcome (Reduction in postoperative opioid requirement)" in my oppinion. The quality of evidence was assesed but not reported. No list of included studies and descriptives is available. Very little to no information regarding effect sizes in the included studies.

Evidence Types	level/Study	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis: (20 studies)</p> <p>To assess the effects of local anaesthetic agent wound infiltration/irrigation and/or abdominal nerve blocks on post-caesarean section pain and the mother's well being and interaction with her baby.</p> <p>Databases: Cochrane Pregnancy and Childbirth Group's Trials Register (contains trials identified from: 1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); 2. weekly searches of MEDLINE;)</p> <p>Search period: Inception - April 2009</p> <p>Inclusion Criteria: Randomised controlled trials of pre-emptive local analgesia during caesarean section.</p> <p>Exclusion Criteria: not described.</p>	<p>Population: Women undergoing caesarean section, either electively or as an emergency.</p> <p>Intervention: 1. Local anaesthetic agent wound infiltration versus placebo/no infiltration 2. Ilioinguinal/iliohypogastric nerve block versus placebo/no treatment 3. Local anaesthetic agent versus other methods of pain relief</p> <p>Comparison: Comparison of different local anaesthetic agent techniques</p>	<p>Primary: 1. Postoperative pain scores 2. Postoperative analgesia requirement 3. Time to first rescue analgesia 4. Postoperative fever 5. Duration of caesarean section 6. Onset of mobilisation 7. Onset of breastfeeding 8. Duration of any breastfeeding 9. Duration of exclusive breastfeeding 10. Minor side effects of the local anaesthetic 11. Major side effects, e.g. central nervous system or cardiovascular 12. Duration of hospital stay 13. Postoperative wound infection 14. Women's pain relief satisfaction 15. Overall satisfaction 16. Occurrence of postnatal depression or neurotic/psychotic disorders 17. Chronic pelvic pain 18. Caregiver satisfaction 19. Cost</p> <p>Secondary: not described.</p>	<p>20 articles included: Bamigboye 2008, Bell 2002, Caulry 2003, Chen 1990, Ganta 1994, Givens 2002, Kumar 1999, Kuppavelamini 1992, Lacrosse 2004, Lavand'homme 2007, Marbaix 2004, McDonnell 2008, Mecklem 1995, Pavy 1994, Pibudak 2004, Rosaeg 1997, Solak 1999, Trotter 1991, Zohar 2002,</p>	
			<p>Results: Results: only summary displayed, rest see article. Twenty studies (1150 women) were included. Women who had caesarean section performed under regional analgesia and had wound infiltration had a decrease in morphine consumption at 24 hours (SMD -1.70mg; 95% confidence interval (CI) -2.75 to -0.94) compared to placebo. In women under general anaesthesia, with caesarean section wound infiltration and peritoneal spraying with local anaesthetic (one study, 100 participants), the need for opioid rescue was reduced (risk ratio (RR) 0.51; 95% CI 0.38 to 0.69). The numerical pain score (0 to10) within the first hour was also reduced (mean difference (MD) -1.46; 95% CI -2.60 to -0.32). Women with regional analgesia who had local anaesthetic and non-steroidal anti-inflammatory cocktail wound infiltration consumed less morphine (one study, 60 participants; MD -7.40 mg; 95% CI -9.58 to -5.22) compared to local anaesthetic control. Women who had regional analgesia with abdominal nerves blocked had decreased opioid consumption (four studies, 175 participants; MD -25.80 mg; 95% CI -50.39 to -5.37). For the outcome of visual analogue scale 0 to 10 over 24 hours, no advantage was demonstrated in the single study of 50 participants who had wound infiltrated with a mixture of local analgesia and narcotics versus local analgesia. Addition of ketamine to the local</p>	

analgesia in women who had regional analgesia does not confer any advantage.

**Author's Conclusion:** Implications for practice: In general, local anaesthesia is of benefit in women having a caesarean section by reduction in opioid consumption. It can be recommended, with consideration to aLordability, as part of the multimodal approach to pain relief.

**Methodical Notes**

**Funding Sources:** Internal sources

• (GJH) ELelective Care Research Unit, University of the Witwatersrand, University of Fort Hare, Eastern Cape Department of Health, South Africa.

External sources

• (GJH) World Health Organization (long-term Institutional Development Grant), Switzerland.

**COI:** AA Bamigboye has conducted a study of ropivacaine wound infiltration and peritoneal spray for caesarean section pain relief as part of a degree program, supervised by GJ Hofmeyr. The study is included in this review.

**Study Quality:** We assessed the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

**Heterogeneity:** We applied tests of heterogeneity between trials, if appropriate, using the I2 statistic. In the event of significant heterogeneity, we used a random-eLects meta-analysis as an overall summary if we determined that this was appropriate.

**Publication Bias:** Not investigated

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

No investigation of publication bias. A number of comparisons only contain a single study.

**Boddy, A. P. et al. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. Anesth Analg. 103. 682-8. 2006**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic Review and Meta-Analysis (16 studies) To evaluate the effects of intraperitoneal local analgesia on early postoperative abdominal pain after laparoscopic cholecystectomy. Databases: MEDLINE, EMBASE, and the Cochrane Library</p> <p>Search period: Inception - 06 / 2005.</p> <p>Inclusion Criteria: Double-blind, randomized comparisons of intraperitoneal LA versus placebo or no treatment, evaluating abdominal pain in the setting of laparoscopic cholecystectomy. Trials combining intraperitoneal LA with other interventions (e.g., port site infiltration or intraperitoneal nonsteroidal antiinflammatory drugs) were included as long as there were comparable treatment and control groups in which the only difference was instillation of intraperitoneal LA.</p>	<p>Population: Patients undergoing laparoscopic cholecystectomy.</p> <p>Intervention: Intraperitoneal local anesthesia (LA)</p> <p>Comparison: Placebo or no treatment.</p>	<p>Primary: Abdominal pain score at 4 h after surgery.</p> <p>Secondary: adverse events.</p> <p>Results: Results: only summary results displayed here due to length, rest see article. 24 randomized, controlled trials assessing intraperitoneal local anesthetic use in laparoscopic cholecystectomy that met inclusion criteria. Of these, 16 studies reported sufficient data to allow pooled quantitative analysis. The weighted mean differences (WMD) in visual analog pain score at 4 h after surgery were pooled using a random effects model. Overall, the use of intraperitoneal local anesthesia resulted in a significantly reduced pain score at 4 h (WMD, -9 mm; 95% confidence interval [CI], -13 to -5). Subgroup analysis suggested that the effect was greater when the local anesthetic was given at the start of the operation (WMD, -13 mm; 95% CI, -19 to -7) compared with instillation at the end (WMD, -6 mm; 95% CI, -10 to -2). No adverse events related to local anesthetic toxicity were reported.</p> <p>Author's Conclusion: Overall, this review does lend limited support to the use of intraperitoneal LA in laparoscopic cholecystectomy as part of a multimodal approach to pain management. The technique seems to be safe and results in a statistically significant reduction in early postoperative</p>	<p>Chundrigar 1993, Rademaker 1994, Joris 1995, Raetzell 1995, Scheinin 1995, Fornari 1996, Fuhrer 1996, Pasqualucci 1996, Szem 1996, Mraovic 1997, Weber 1997, Tsimoyiannis 1998, Elfberg 2000, Kolsi 2000, Zmora 2000, Lee 2001, Jiranantararat 2002, Labaille 2002, Maestroni 2002, Karadeniz 2003, Lepner 2003, Paulson 2003, Razek 2003, Ng 2004.</p>

**Exclusion Criteria:** Trials in which infusions of LA were administered after the patient had recovered from anesthesia were excluded. Papers that could not be supplied by the British Library were not included.

abdominal pain. It may be of particular benefit when the operation is planned as an ambulatory procedure to improve same-day discharge rates. Finally, there is some evidence to suggest that LA may be more effective if used at a larger strength and if at least some is instilled before any dissection.

**Methodical Notes**

**Funding Sources:** not disclosed.

**COI:** not disclosed.

**Study Quality:** The methodological quality of each eligible study was assessed using a 3-item, 5-point scale, which has previously been validated (3). Studies described as randomized were given either 1 or 2 points if the method of randomization was described and was appropriate. One point was deducted if randomization was inappropriate. Studies described as doubleblind were either given 1 or 2 points if the method of blinding was described and was appropriate. One point was deducted if blinding was inappropriate. If the numbers were described and reasons for withdrawals offered, a further point was given. As only randomized, double-blind trials were included, the minimum possible score for each study was 2 and the maximum 5.

**Heterogeneity:** "Because there was considerable clinical heterogeneity among trials (different quantities and concentrations of different LAs were used and different postoperative analgesia regimens were used), pooled analysis was performed using a random effects model."

"As expected, there was a significant degree of heterogeneity among the studies, as demonstrated by an I2 value of 74.8% (I2 is a measure used to quantify heterogeneity and represents the percentage of the variability that is caused by heterogeneity rather than sampling error: a value more than 50% may be considered to represent substantial heterogeneity)."

**Publication Bias:** Not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic Review and Meta-Analysis.

Downgrade to evidence level 2.

Publication bias not investigated. No disclosures of financial ties or potential conflicts of interest. Substantial heterogeneity limits the implications of the meta-analysis. Relatively old meta-analysis, despite little overlap with other identified articles on the same population/intervention

Choi, G. J. et al. Effect of intraperitoneal local anesthetic on pain characteristics after laparoscopic cholecystectomy. *World J Gastroenterol.* 21. 13386-95. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p><b>Study type:</b> Systematic review and meta-analysis (39 RCTs)</p> <p>To systematically evaluate the effect of intraperitoneal local anesthetic on pain characteristics after laparoscopic cholecystectomy (LC).</p> <p><b>Databases:</b> independently performed database searches using EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL).</p> <p><b>Search period:</b> Inception - 2015.</p> <p><b>Inclusion Criteria:</b> Randomized controlled trials (RCTs) in English that compared the effects of the intraperitoneal administration of local anesthetic (IPLA group) with placebo or no treatment (control group) on pain after elective LC under general anesthesia were included. Studies that combined IPLA with other interventions were included if there were comparable intervention and control groups in which the only difference was the use of IPLA. Studies with more than one IPLA or control group were included if there were comparable groups that met the inclusion criteria.</p> <p><b>Exclusion Criteria:</b> not described.</p>	<p><b>Population:</b> Elective Laparoscopic cholecystectomy (LC) patients.</p> <p><b>Intervention:</b> intraperitoneal administration of local anesthetic (IPLA group)</p> <p><b>Comparison:</b> placebo or no treatment (control group).</p>	<p><b>Primary:</b> Combined scores of abdominal, visceral, parietal, and shoulder pain after LC at multiple time points.</p> <p><b>Secondary:</b> none described.</p> <p><b>Results:</b> Results: onlys summar reported here, due to length, rest see article. We included 39 studies of 3045 patients in total. The administration of intraperitoneal local anesthetic reduced pain intensity in a resting state after laparoscopic cholecystectomy: abdominal [standardized mean difference (SMD) = -0.741; 95%CI: -1.001 to -0.48, P &lt; 0.001]; visceral (SMD = -0.249; 95%CI: -0.493 to -0.006, P = 0.774); and shoulder (SMD = -0.273; 95%CI: -0.464 to -0.082, P = 0.097). Application of intraperitoneal local anesthetic significantly reduced the incidence of shoulder pain (RR = 0.437; 95%CI: 0.299 to 0.639, P &lt; 0.001). There was no favorable effect on resting parietal or dynamic abdominal pain.</p> <p><b>Author's Conclusion:</b> "In conclusion, IPLA as an analgesic adjuvant in patients undergoing LC exhibited a favorable effect on postoperative abdominal, visceral, and shoulder pain during a resting state"</p>	<p>39 articles included, see article due to length.</p>

**Methodical Notes**

Funding Sources: not described.

COI: The authors deny any conflict of interest.

**Study Quality:** Risk of bias assessment Two authors independently assessed the quality of eligible studies using the Cochrane Collaboration's Tool for assessment of risk of bias.

"Second, the quality of the included studies was limited. Notwithstanding this limitation, our study was the first meta-analysis to evaluate the effect of IPLA on pain characteristics after LC application using a rigorous methodology."

**Heterogeneity:** "The pooled risk ratio (RR) or standardized mean difference (SMD) and 95% CIs were calculated for each outcome. We used the  $\chi^2$  test for homogeneity and the I<sup>2</sup> test for heterogeneity. We regarded a level of 10% significance ( $P < 0.100$ ) in the  $\chi^2$  statistic or an I<sup>2</sup> greater than 50% as considerable heterogeneity, and we used the Mantel-Haenszel random-effect model. Otherwise, we applied the Mantel-Haenszel fixed-effect model."

**Publication Bias:** Publication bias was evaluated using a funnel plot and Egger's linear regression test. If the funnel plot was asymmetrical or the P value was  $< 0.100$  by the Egger's test, we considered the presence of a publication bias and performed trim and fill analyses.

"A funnel plot was used for every comparison, and all data displayed a symmetrical appearance. The results of Egger's test indicated that publication bias was unlikely for all outcomes: resting abdominal pain ( $P = 0.076$ ); dynamic abdominal pain ( $P = 0.416$ ); visceral pain ( $P = 0.143$ ); parietal pain ( $P = 0.508$ ); shoulder pain severity ( $P = 0.683$ ); and incidence of shoulder pain ( $P = 0.239$ ). We performed trim and fill analyses on the assumption that publication bias was evident for resting abdominal pain to evaluate the influence of publication bias. The result of resting abdominal pain remained significant (SMD =  $-0.914$ ; 95%CI:  $-1.182$  to  $-0.646$ ), which suggests that publication bias was unlikely."

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

Downgrade to evidence level 2.

Risk of bias investigated using Cochrane RoB tool, but not reported for individual studies. High heterogeneity, due to differences in dose, concentration, or volume of IPLA, the timing or site of IPLA administration, the volume and pressure of pneumoperitoneum, and the analgesic method during the postoperative period.

Hamill, J. K. et al. Analgesic effect of intraperitoneal local anesthetic in surgery: an overview of systematic reviews. *J Surg Res.* 212. 167-177. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review of systematic reviews. (9 included articles)</p> <p>To compare the efficacy of IPLA between different types of procedure and to formulate GRADE recommendations for the use of IPLA.</p> <p>Databases: MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database</p> <p>Search period: Inception - 01 / 2016.</p> <p>Inclusion Criteria: Eligible participants were people of any age undergoing abdominal surgery, without restriction, that is, whether their surgery was laparoscopic or open or general as opposed to gynecological. The primary outcome was the postoperative pain score taken at 6 h or nearest time point. The 6-h time point was chosen to reflect the expected duration of action of "long-acting" local anesthetics such as bupivacaine or ropivacaine. Because the focus of this review was to compare the efficacy of IPLA across a range of procedures, we chose one outcome measure that would well reflect postoperative pain, that is, self-reported pain scores. Eligible individual studies, identified from the included reviews, were RCTs of IPLA compared with control, in which at least one outcome was pain score, that is, the eligibility criteria for individual RCTs reflected eligibility criteria for reviews.</p> <p>Exclusion Criteria: none described.</p>	<p>Population: Participants of any age undergoing abdominal surgery, without restriction, that is, whether their surgery was laparoscopic or open or general as opposed to gynecological.</p> <p>Intervention: IPLA</p> <p>Comparison: control not defined (likely placebo / no intervention or std anaesthesia)</p>	<p>Primary: postoperative pain score taken at 6 h or nearest time point</p> <p>Secondary: -</p> <p>Results: Only summary results presented, due to length. Searches uncovered nine systematic reviews. This study included randomized trials numbered 76, representing 4000 participants, 2022 in IPLA and 1978 in control groups. Six reviews scored at low risk of bias and three at high risk. Overall, the GRADE quality of evidence was moderate (Grade B). The quality of evidence was downgraded for high heterogeneity. Meta-analysis demonstrated that IPLA reduced the mean pain score (0-10 scale) by 0.95 point (95% confidence interval: 0.73-1.17). Excluding laparoscopic cholecystectomy, the effect size increased to 1.52 (95% confidence interval: 1.15-1.88). Heterogeneity was high overall at I<sup>2</sup> ¼ 91.7% but on excluding laparoscopic cholecystectomy trials reduced to I<sup>2</sup> ¼ 31.3%.</p>	<p>9 systematic review included, which includes 76 studies, for list see article.</p>
<p>Author's Conclusion: Instillation of local anesthetic into the peritoneal cavity could be considered an option for early postoperative analgesia in</p>			

certain laparoscopic operations. The small effect size and large heterogeneity in laparoscopic cholecystectomy lead to a weak recommendation; conversely, the clinically significant effect and low heterogeneity in other conditions suggest that surgeons could consider IPLA in their practice and should undertake further research in a variety of procedures.

## Methodical Notes

**Funding Sources:** The authors declare that they have no conflict of interest. No funding was received for the conduct of this study.

**COI:** see funding.

**Study Quality:** The GRADE question asked, "should IPLA be used for early analgesia after abdominal surgery?" Assessment of quality of evidence was by study limitations, inconsistency (heterogeneity), indirectness, imprecision, publication bias, and size of effect. Assessment of the strength of recommendation was by the quality of evidence, the balance between desirable and undesirable effects, patient values & preferences, and wise use of resource.

"Overall, the GRADE quality of evidence was moderate (Grade B). The quality of evidence was downgraded for high heterogeneity. The GRADE recommendation for IPLA, for pooled procedures, was 2B, that is, "weak recommendation, moderate quality evidence." The recommendation was downgraded for the small effect size. The GRADE quality of evidence for IPLA in laparoscopic gastric or laparoscopic gynecological procedures was high (Grade A), and the GRADE recommendation was 1A, that is, "strong recommendation, high quality evidence."

**Heterogeneity:** Heterogeneity between studies was assessed by Cochran's c2 test<sup>15</sup> and inconsistency (variation across studies caused by heterogeneity) by the I2 test,<sup>16,17</sup> with c2 P < 0.1 suggesting "significant" heterogeneity, and I2 <30%, 30%-60%, and >60% suggesting "low," "moderate," and "high" inconsistency respectively

**Publication Bias:** Funnel plots were visually inspected for asymmetry, and a weighted linear regression test of the treatment effect on the standard error was used to test for publication bias.

"The funnel plot had a symmetric appearance. Statistical analysis for asymmetry showed that the treatment effect did not depend on precision (t = 1.68, P = 0.097), thus indicating no publication bias."

### Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.

High heterogeneity for main outcome postoperative pain score overall (I2=92%) and for the subset of laparoscopic cholecystectomy (I2=92%).

Hamilton, T. W. et al. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. *Cochrane Database Syst Rev.* 2. CD011419. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review (9 studies)</p> <p>To assess the analgesic efficacy and adverse effects of liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain.</p> <p>Databases: On 13 January 2016 we searched CENTRAL, MEDLINE, MEDLINE In-Process, Embase, ISI Web of Science and reference lists of retrieved articles. We obtained clinical trial reports and synopses of published and unpublished studies from Internet sources,</p>	<p><b>Population:</b> We included all trials with participants aged 18 years and older undergoing elective surgery at any surgical site, without restriction on any co-morbidities.</p> <p><b>Intervention:</b> We included all double-blind randomised controlled trials (RCTs) that compared the effects of a single dose of liposomal bupivacaine infiltrated at the surgical site. We considered studies reporting on pre-emptive, intraoperative and postoperative wound infiltration eligible for inclusion provided the drug was administered not earlier than 30 minutes prior to the procedure or later than 30 minutes after wound closure.</p> <p><b>Comparison:</b> Placebo or other types of analgesia delivered systemically, via local</p>	<p><b>Primary:</b></p> <ul style="list-style-type: none"> <li>Cumulative pain intensity assessed on a 100 mm visual analogue scale (VAS) over the initial 72 hours following surgery, at rest or with activity. However, we considered all types of pain scales with standardisation of pain intensity data described by other means than a 100 mm VAS, where possible.</li> <li>Serious adverse events, specifically incidence of cardiac events and incidence of wound complications within 30 days of surgery.</li> </ul> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>Mean pain score, at rest or with activity, assessed on a 100 mm VAS at 12, 24, 48, 72 and 96 hours following surgery. We considered all types of pain scales with standardisation of pain intensity data described by other means than a 100 mm VAS, where possible.</li> <li>Time to first postoperative opioid dose over initial 72 hours.</li> <li>Total postoperative opioid consumption over first 72 hours.</li> <li>Percentage of participants not requiring postoperative opioids over initial 72 hours.</li> <li>Health economics assessed using a recognised health economic technique.</li> <li>Incidence of adverse events within 30 days of</li> </ul>	<p>9 studies included:</p> <p>Bramlett 2012, Golf 2011, Gorfine 2011, Haas 2012, Langford 2008, NCT <a href="#">00744848</a>, NCT <a href="#">00745290</a>, Smoot 2012, White 2009.</p>

and searched clinical trials databases for ongoing trials.

Search period:  
Previous version - 01/2016.

Inclusion Criteria:  
Randomised, double-blind, placebo- or active-controlled clinical trials in people aged 18 years or over undergoing elective surgery, at any surgical site, were included if they compared liposomal bupivacaine infiltration at the surgical site with placebo or other type of analgesia.

Exclusion Criteria:  
Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number); studies that did not conceal allocation (e.g. open list). We excluded studies that were not double blind; studies where outcome assessment was not blinded.

infiltration, perineural injection, or epidural or subarachnoid (spinal) routes.

surgery.

• Patient-reported outcomes, using validated outcome scores, at any time point following surgery.

Results: Study overview: 9 studies that met inclusion criteria for this review. Four Phase II dose-escalating/de-escalating studies, designed to evaluate and demonstrate efficacy and safety, presented pooled data which could not be used in this analysis. Of the remaining 5 studies two were placebo controlled and three used bupivacaine hydrochloride as a control. Compared to placebo one study reported a lower cumulative pain score 0 to 72 hours after surgery, two studies reported a longer time to first postoperative opioid, and one study reported a lower cumulative opioid consumption 0 to 72 hours after surgery associated with the use of liposomal bupivacaine.

Results: only summary results displayed here, rest see article.

Compared to bupivacaine hydrochloride two studies found no difference in the cumulative pain score 0 to 72 hours after surgery associated with the use of liposomal bupivacaine, and one study reported a lower mean pain score at 12 hours, but not at 24, 48 or 72 hours postoperatively. Three studies reported the number of participants not requiring postoperative opioids, however significant heterogeneity ( $I^2 = 92\%$ ) was observed, limiting further analysis. Data comparing liposomal bupivacaine with femoral nerve block were not available for inclusion in the analysis.

Of the five parallel-arm studies which did not have an adaptive design assessing liposomal bupivacaine against either placebo or bupivacaine hydrochloride, no studies reported health economic assessments or patient-reported outcomes other than pain. Nausea, constipation and vomiting were the most commonly reported adverse events. Data regarding cardiac events and wound complications were not reported. No withdrawals were reported to be due to drug-related adverse events.

Using GRADE we considered the quality of evidence to be very low to moderate with further research considered very likely to have an important impact on our confidence in the estimate of effect. This assessment of quality was predominantly due to sparseness of data as well as a high risk of bias in some of the included studies.

Liposomal bupivacaine does appear to have efficacy in reducing postoperative pain compared to placebo when infiltrated at the surgical site, but, at present the limited evidence does not demonstrate superiority to bupivacaine hydrochloride. Due to the low quality and volume of evidence our confidence in the effect estimate is limited and the true effect may be substantially different from our estimate.

Author's Conclusion: General Implications

Liposomal bupivacaine does appear to have efficacy in reducing postoperative pain compared to placebo when infiltrated at the surgical site, however, at present the limited evidence does not demonstrate superiority to bupivacaine hydrochloride. We assessed the quality of the evidence as moderate to very low and as such our confidence in the effect estimate is limited and the true effect may be substantially different from our estimates.

For clinicians Further evidence as the clinical and cost effectiveness of liposomal bupivacaine infiltration at the surgical site is required as, due to the quality of evidence, the current data do not support or refute the use of liposomal bupivacaine

infiltration at the surgical site for the management of postoperative pain.

**Methodical Notes**

**Funding Sources:** Internal sources • No sources of support supplied  
 External sources • National Institute for Health Research, UK, Other. TWH is supported by the NIHR Biomedical Research Centre, based at Oxford University Hospitals Foundation Trust, Oxford

**COI:** Authors declared funding from NIHR, consultatn, funding from Orthopeadic implant manufacturing companies.

**Study Quality:** Quality evaluated by Cochrane risk of bias tool. Overall quality evaluated by GRADE summary of findings table for each endpoint.

Overall quality of the evidence rated as moderate to very low.

**Heterogeneity:** We examined the heterogeneity of included studies, where possible, using the I2 statistic (Higgins 2003) as described in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011). Where there was substantial heterogeneity (that is I2 greater than 85%) we did not attempt pooled analysis. Had it been possible to perform meta-analysis, as we expected a degree of variability among the eligible studies in terms of the measurement scale used and the subjectivity of the outcome, we planned to use a random-eDeacts model.

**Publication Bias:** We assessed for publication bias, due to non-reporting of negative studies, by contacting the principal investigators of unpublished trials registered as completed on trial registries. As there were fewer than 10 studies included we did not explore publication bias by means of a funnel plot.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

Unclear why studies were included in which control was not placebo (surgical site infiltration of bupivacaine hydrochloride), despite the eligibility criteria. No meta-analysis was performed.

**Hong, S. S. et al. Effect of Continuous Local Anesthetic in Post-Cardiac Surgery Patients: A Systematic Review. Pain Med. 19. 1077-1090. 2018**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis</p> <p>To determine the effect of CLA infusion post cardiac surgery on pain, time to ambulation, severe adverse events, patient satisfaction, time to extubation, length of stay in the intensive care unit and in the hospital, total narcotic consumption, and pulmonary function.</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; CINAHL; Allied and Complementary Medicine (AMED); and PsycINFO;</p>	<p><b>Population:</b> Trials including patients age 18 years or older undergoing cardiac surgery, valve repair/replacement, combined coronary artery bypass graft surgery (CABG) and valve surgery, aortic arch repair, or any cardiac surgery via sternotomy and having continuous local anesthetic infusion compared with either saline infusion, no infusion, or usual care as postoperative analgesia.</p> <p><b>Intervention:</b> CLA infusion in cardiac surgery performed via sternotomy. The CLA infusion must have been at the site of the sternotomy wound, either tunnelled parasternally or adjacent to the sternotomy wound. The medication for CLA infusion could be any local anesthetic agent. Other analgesic supplements such as opioids and nonsteroidal antiinflammatory drugs (NSAIDs) were allowed. The precise nature of anesthetic (medication, rate, dosage, location of the catheter) was recorded wherever possible.</p> <p><b>Comparison:</b> Either a placebo group with same infusion device using saline infusion or a control group using patient-controlled analgesia (PCA) with opioids or local anesthetics</p>	<p><b>Primary:</b> 1. Pain scores at rest, during movement, during or after physiotherapy sessions, or at any other point in time 2. Distance walked or any other measures of activity 3. Severe adverse events, such as wound infection, deep sternal wound infection, toxicity to the infusion, postoperative complication related to the technique of insertion of the delivery device, or local anesthetics</p> <p><b>Secondary:</b> 1. Patient satisfaction with pain management 2. Time to extubation 3. Length of intensive care unit (ICU) stay 4. Length of hospital stay 5. Total narcotic consumption, PCA usage, other pain medication 6. Pulmonary function</p> <p><b>Results:</b> Results: only summary displayed here due to length and number of outcomes: 10 eligible trials with a total of 546 participants were identified. Meta-analyses showed that CLA infusion significantly reduced the total mean visual analog pain score at 72 hours (mean difference [MD] 5 -14.31mm, 95% confidence interval [CI] 5 -25.59 to -3.03); time to ambulation (MD 5 -2.81 hours, 95% CI 5 -5.23 to -0.4); morphine requirement (MD 5 -10.19 mg, 95% CI 5 -11.80 to -8.58) but did not reduce time to ambulate to chair (MD 5 -1.65 hours, 95% CI 5 -4.04 to 0.74); time to extubation (MD 5 -0.18 hours, 95% CI 5 -1.24 to 0.89); length of ICU stay (MD50.9 hours, 95% CI 5 -2.96 to 4.75); and hospital length of stay (MD 5 -0.59 days, 95% CI 5 -1.24 to 0.07). There were insufficient data to perform a meta-analysis on severe adverse events, patient satisfaction, or pulmonary function.</p> <p><b>Author's Conclusion:</b> In conclusion, this is the first systematic review with meta-analyses investigating the effectiveness of CLA infusion adjacent to the sternal wound after cardiac surgery. CLA infusion reduced pain at 72 hours, reduced the time to commencement of ambulation, and reduced morphine equivalent at 48 hours. However, it should be noted that the meta-analyses are based on the relatively small numbers of studies that could be included in the meta-analyses. CLA infusion did not reduce time to extubation or length of</p>	<p>10 articles included: Dowling 2003, Magnano 2005, White 2003, Ghavidel 2009, Langley 2009, Eljezi et al. 2012, Abbasi 2012, Agarwal 2013, Dignan 2014, Nasr 2015.</p>



<p>Search period: Inception - to June - August 2016.</p> <p>Inclusion Criteria: RCTs on adults undergoing cardiac surgery, comparing CLA infusion with placebo saline infusion regarding pain, activity and severe adverse events.</p> <p>Exclusion Criteria: inclusion criteria not met.</p>	<p>agents or any other method of pain relief.</p>	<p>stay in the ICU or in hospital. CLA infusion may be an effective pain relief management in the early postoperative period; however, more data are required to analyze the effects of CLA infusion on severe adverse events, patient satisfaction, and pulmonary function.</p>	
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<p><b>Methodical Notes</b></p>
<p><b>Funding Sources:</b> This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.</p> <p><b>COI:</b> The authors have no conflicts of interest to declare.</p> <p><b>Study Quality:</b> We evaluated the methodological quality of the studies by the type of randomization, sequence generation for randomization, allocation concealment, blinding, and completeness of trial data. "The quality assessment (bias) of included studies is shown in Figure 2. All trials had low risk in selective reporting, and blinding occurred in 70% of included trials. Random sequence occurred in 60% of trials, concealed allocation occurred in 40% of the trials, and 60% of trials had low risk in incomplete data."</p> <p><b>Heterogeneity:</b> We performed a test for heterogeneity of studies included in the meta-analyses. For continuous variables of pain score, walking distance, patient satisfaction, length of stay in ICU and hospital, time to extubation, total narcotic consumption or morphine equivalent, and pulmonary function, either the mean change from baseline (95% confidence interval [CI]) or the mean postintervention values and standard deviation for each group were used for the meta-analyses. Odds ratios were calculated for binary outcomes such as failure of regimen or adverse events. Subgroup analysis was conducted, if required, to explore possible sources of heterogeneity.</p> <p><b>Publication Bias:</b> Publication bias not investigated.</p> <p><b>Notes:</b> Oxford level of evidence: 1 Publication bias not investigated. No reporting on individual study quality.</p>

<p>Joshi, G. P. et al. Evidence-based management of postoperative pain in adults undergoing open inguinal hernia surgery. <i>Br J Surg.</i> <b>99.</b> 168-85. 2012</p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review and meta-analysis (79 studies)</p> <p>The aim of this systematic review was to evaluate the available literature on the management of pain after open hernia surgery.</p> <p>Databases: Embase and MEDLINE.</p> <p>Search period: 1966 and March 2009.</p> <p>Inclusion Criteria: Randomized controlled trials (RCTs) in the English language assessing analgesic and anaesthetic</p>	<p>Population: Adult undergoing inguinal hernia surgery,</p> <p>Intervention: Analgesic and anaesthetics, not specified.</p> <p>Comparison: no comparator specified.</p>	<p>Primary: Postoperative pain outcomes (pain scores and supplementary analgesic requirements)</p> <p>Secondary: Adverse effects</p> <p>Results: Results: only summary results displayed due to length, rest see article.</p> <p>Of the 334 randomized studies identified, 79 were included. Quantitative analysis suggested that regional anaesthesia was superior to general anaesthesia for reducing postoperative pain. Spinal anaesthesia was associated with a higher incidence of urinary retention and increased time to homereadiness compared with regional anaesthesia.</p> <p>Author's Conclusion: Field block with, or without wound infiltration, either as a sole anaesthetic/analgesic technique or as an adjunct to general anaesthesia, is recommended to reduce postoperative pain. Continuous local anaesthetic infusion of a surgical wound provides a longer duration of analgesia. Conventional non-steroidal anti-inflammatory drugs or cyclo-oxygenase 2-selective inhibitors in combination with</p>	<p>79 articles included: for list see article.</p>

interventions in adult inguinal hernia surgery, and reporting pain on a linear analogue, verbal or numerical rating scale, were included.

**Exclusion Criteria:**  
Laparoscopic inguinal hernia repair was excluded.

paracetamol, administered in time to provide sufficient analgesia in the early recovery phase, are optimal. In addition, weak opioids are recommended for moderate pain, and strong opioids for severe pain, on request.

**Methodical Notes**

**Funding Sources:** Pfizer provided financial support for the editorial assistance provided by Choice Pharma. This paper makes no specific recommendations about the use of any medical products, drugs or equipment manufactured by Pfizer or by any of its subsidiaries. G.P.J., H.K. and N.R. have received honoraria for consultancy and/or presentation from Pfizer.

**COI:** The authors declare no other conflict of interest.

**Study Quality:** The quality of available evidence was graded from A-D. Statistical analyses and patient follow-up assessment indicated whether statistical analyses were reported and whether patient follow-up was greater or less than 80 per cent. Allocation concealment assessment indicated whether there was adequate prevention of foreknowledge of treatment assignment by those involved in recruitment (A, adequate; B, unclear; C, inadequate; D, not used). Numerical scores (total 1–5) for study quality were assigned using the method proposed by Jadad and colleagues to indicate whether a study reported appropriate randomization, double-blinding and statements of possible withdrawals. Additional study quality assessment included an assessment of how closely the study report met the requirements of the Consolidated Standards of Reporting Trials (CONSORT) statement.

**Heterogeneity:** RevMan software performed heterogeneity analyses; data that were not significantly heterogeneous ( $P > 0.100$ ) were analysed using a fixed-effects model, and heterogeneous data ( $P \leq 0.100$ ) using a random-effects model. Only one meta-analysis was performed, here heterogeneity was low  $I^2=15\%$ .

**Publication Bias:** No investigation of publication bias.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis  
Downgrade to evidence level 2.

No investigation of publication bias. No information on included studies. Only a single meta-analysis was carried out (regional vs. spinal anaesthesia regarding urinary retention. No individual study quality evaluation reported.

**Kahokehr, A. et al. Systematic review and meta-analysis of intraperitoneal local anaesthetic for pain reduction after laparoscopic gastric procedures. Br J Surg. 98. 29-36. 2011**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level: 1</b></p> <p><b>Study type:</b> Systematic review and meta-analysis (5 studies) To investigate the clinical effects of intraperitoneal local anaesthetic (IPLA) in laparoscopic gastric procedures. <b>Databases:</b> Cochrane Central Register of Controlled Trials, the Cochrane Library, MEDLINE, PubMed, Embase and CINAHL. <b>Search period:</b> Inception to 02 / 2010.</p> <p><b>Inclusion Criteria:</b> Publications were selected for review if they investigated, in a double-blinded randomized study, the effects of IPLA (treatment) versus placebo (control) on pain outcomes in adults undergoing laparoscopic gastric procedures. For studies that used IPLA both before and after dissection, only pre-dissection results were included in the meta-analysis owing to the pre-emptive nature of the intervention.</p> <p><b>Exclusion Criteria:</b> Open surgery, concomitant use of preperitoneal or abdominal wall (incisional/port-site) local anaesthetic, and concomitant use of intramuscular or intravenous analgesia unless IPLA use was being investigated</p>	<p><b>Population:</b> Adults undergoing laparoscopic gastric procedures.</p> <p><b>Intervention:</b> Intraperitoneal local anaesthetic (IPLA) (treatment)</p> <p><b>Comparison:</b> Placebo (control)</p>	<p><b>Primary:</b> Abdominal pain scores measured on a visual analogue scale (0–100 mm or 0–10 cm) and incidence of shoulder tip pain.</p> <p><b>Secondary:</b> Postoperative opioid use.</p> <p><b>Results:</b> Results: only summary results displayed here due to length, rest see article 5 randomized controlled trials in laparoscopic gastric procedures were identified for review. There was no significant heterogeneity between the trials (<math>\chi^2 = 10.27</math>, 10 d.f., <math>P = 0.42</math>, <math>I^2 = 3\%</math>). Based on meta-analysis of trials, there appeared to be reduced abdominal pain intensity (overall mean difference in pain score <math>-1.64</math>, 95 per cent confidence interval (c.i.) <math>-2.09</math> to <math>-1.19</math>; <math>P &lt; 0.001</math>), incidence of shoulder tip pain (overall odds ratio 0.15, 95%CI. 0.05 to 0.44; <math>P &lt; 0.001</math>) and opioid use (overall mean difference <math>-3.23</math>, <math>-4.81</math> to <math>-1.66</math>; <math>P &lt; 0.001</math>).</p> <p><b>Author's Conclusion:</b> There is evidence in favour of IPLA in laparoscopic gastric procedures for reduction of abdominal pain intensity, incidence of shoulder pain and postoperative opioid consumption.</p>	<p>5 articles included: Cunniffe 1998, Palmes 2007, Symons 2007, Sherwinter 2008, Alkhamesi 2008, Peach 2008.</p>

alone as part of a multimodal regimen with a placebo-controlled comparison group.

**Methodical Notes**

**Funding Sources:** This research was conducted during tenure of the Ruth Spencer fellowship from the Auckland Medical Research Foundation held by A.K. and S.S.

**COI:** The authors declare no conflict of interest.

**Study Quality:** Two authors examined all retrieved articles independently; any disagreement over inclusion or exclusion was discussed with a third author and a consensus reached. The methodological quality of randomized clinical trials was assessed using the Jadad criteria.

3 of 5 studies were graded as high quality, 2 were moderate quality.

**Heterogeneity:** A  $\chi^2$  test for statistical heterogeneity was performed, with  $P < 0.100$  being considered statistically significant. Finally, I<sup>2</sup> statistics were used to assess clinical heterogeneity<sup>19</sup>. If statistical heterogeneity was identified, sensitivity analysis was performed to detect small study effects by comparison of the fixed- and random-effects estimates of the intervention. In the event of moderate or high clinical heterogeneity (defined as I<sup>2</sup> at least 50 per cent), methodological subgroup analysis was performed<sup>19</sup> in which trials with a Jadad score of 4 and 5 rated were grouped together as 'high-quality' studies and all other trials grouped as 'low-quality' trials to investigate the cause further. Study weight was by sample size.

"As overall heterogeneity was low and not significant, the authors believe the results of this meta-analysis to be valid despite the variety of gastric procedures"

**Publication Bias:** First, publication bias was tested using the funnel plot graphical exploration method. Funnel plots are reported to be symmetrical.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

**Kjaergaard, M. et al. Wound infiltration with local anesthetics for post-operative pain relief in lumbar spine surgery: a systematic review. Acta Anaesthesiol Scand. 56. 282-90. 2012**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level: 1</b></p> <p><b>Study type:</b> Systematic review (9 studies) To evaluate the effect of wound infiltration with local anesthetics on post-operative pain, supplemental analgesic consumption, time to first analgesic request, as well as on side effects in patients undergoing lumbar spine surgery by using evidence from all relevant double-blind, randomized and controlled trials.</p> <p><b>Databases:</b> Medline, a Google Scholar and a Cochrane Library, Clinicaltrials.gov Inception - 06 / 2011.</p> <p><b>Search period:</b> Inception - 06 / 2011.</p> <p><b>Inclusion Criteria:</b> Double-blind, randomized and controlled trials comparing wound infiltration (skin infiltration, soft tissue infiltration or paraspinal muscle infiltration) using local anesthetics (experimental intervention group) with placebo/no treatment (control group) in adult patients (&gt; 17 years) undergoing lumbar spine surgery (lumbar decompression, lumbar discectomy, lumbar arthrodesis or lumbar laminectomy) in general anesthesia. Only studies in English presenting data on pain [visual analog scale (VAS) or similar scores], supplemental post-operative analgesic consumption and/or time to first analgesic request were included. Methods of the analysis and inclusion criteria were specified in advance but not documented in a protocol.</p> <p><b>Exclusion Criteria:</b> not provided.</p>	<p><b>Population:</b> Adult patients (&gt; 17 years) undergoing lumbar spine surgery (lumbar decompression, lumbar discectomy, lumbar arthrodesis or lumbar laminectomy).</p> <p><b>Intervention:</b> Infiltration (skin infiltration, soft tissue infiltration or paraspinal muscle infiltration) using local anesthetics.</p> <p><b>Comparison:</b> Placebo / no treatment</p>	<p><b>Primary:</b> Pain scores</p> <p><b>Secondary:</b> Supplemental opioid consumption, time to first analgesic request, adverse effects.</p> <p><b>Results:</b> Results: only summary results displayed here due to length. Nine trials including 12 comparisons and 529 patients met the inclusion criteria. Ten comparisons presented data on pain scores. In only three of these 10 comparisons (30%), a reduction in pain score using local anesthetic infiltration was observed averaging between 8 and 40 mm on a 100 mm visual analog scale. In six out of 12 comparisons, the local anesthetic infiltration significantly reduced the supplemental opioid consumption after surgery. Observed reductions in analgesic consumption over the first 24 h averaged between 2.5 mg and approximately 15 mg of morphine. Data on opioid-related adverse effects were incomplete and difficult to interpret.</p> <p><b>Author's Conclusion:</b> "Interpretation of the results was difficult because of diversity of the studies. However, clinical significance was in general questionable, with only a few trials showing a small or a modest reduction in pain intensity, which was observed mainly immediately after the operation. Similarly, although more frequently observed, only a minor and probably not clinically relevant reduction in opioid consumption was shown."</p>	<p><b>9 articles included:</b> Ersayli 2006, Gurbert 2008, Steel 1998, Mack 2001, Esmail 2008, Milligan 1993, Teddy 1981, Cherian 1997, Yörükoglu 2005.</p>

**Methodical Notes**

Funding Sources: Not disclosed.

COI: Not disclosed.

**Study Quality:** Each report that met the inclusion criteria was read and scored independently by two of the authors using the Oxford quality score, a three-item, 1–5 quality scale to assess the adequacy of randomization as well as blinding and to assess the description of withdrawals. As there was a priori agreement that reports without randomization and double-blinding would be excluded, the minimum score of an included trial was 2, and the maximum score was 5.

"All trials in this review were randomized with the median Oxford quality score being 4, and so selection bias should not have been a problem. Most trials (eight out of 12 comparisons) reported a positive outcome of either opioid reduction or pain score improvement, and publication bias cannot be ruled out, which in that case probably would strengthen the tendency to a negative interpretation of the results of the review."

**Heterogeneity:** Not applicable, since no meta-analysis was performed.

**Publication Bias:** Discussed, but not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

No disclosure of interests, financial ties.

Loizides, S. et al. Wound infiltration with local anaesthetic agents for laparoscopic cholecystectomy. *Cochrane Database Syst Rev.* . CD007049. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systmatic review and meta-analysis: 19 studies</p> <p>To assess the benefits and harms of local anaesthetic wound infiltration in patients undergoing laparoscopic cholecystectomy and to identify the best method of local anaesthetic wound infiltration with regards to the type of local anaesthetic, dosage, and time of administration of the local anaesthetic.</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Science Citation Index Expanded.</p> <p>Search period: Inception - 02 / 2013 to identify studies of relevance to this review.</p> <p>Inclusion Criteria: Only</p>	<p>Population: People undergoing laparoscopic cholecystectomy irrespective of age, elective or emergency surgery, and the reason why the laparoscopic cholecystectomy was performed</p> <p>Intervention: • Wound infiltration compared with no wound infiltration or wound infiltration with normal saline. • Different local anaesthetics used for wound infiltration (eg, bupivacaine versus lignocaine). • Different doses of the same local anaesthetic. • Different times of wound infiltration (eg, before incision compared with after incision).</p> <p>Comparison: see intervention</p>	<p>Primary: 1. Mortality. 2. Serious adverse events 3. Patient quality of life</p> <p>Secondary: 1. Hospital stay 2. Pain (overall pain) at different time points (4 to 8 hours and 9 to 24 hours) using a visual analogue scale. 3. Return to activity. 4. Return to work.</p> <p>Results: Study overview: Only summary results displayed here, rest see article. 26 trials fulfilled the inclusion criteria of the review, all but one (n=30 participants) were at high risk of bias. 19 trials with 1263 randomised participants provided data for this review.</p> <p>Results: Most trials included only low anaesthetic risk people undergoing elective laparoscopic cholecystectomy. 17 trials randomised a total of 1095 participants to local anaesthetic wound infiltration (587 participants) versus no local anaesthetic wound infiltration (508 participants). Various anaesthetic agents were used but bupivacaine was the commonest local anaesthetic used. There was no mortality in either group in the seven trials that reported mortality (0/280 (0%) in local anaesthetic infiltration group versus 0/259 (0%) in control group). The effect of local anaesthetic on the proportion of people who developed serious adverse events was imprecise and compatible with increase or no difference in serious adverse events (seven trials; 539 participants; 2/280 (0.8%) in local anaesthetic group versus 1/259 (0.4%) in control; RR 2.00; 95% CI 0.19 to 21.59; very low quality evidence). None of the serious adverse events were related to local anaesthetic wound infiltration. None of the trials reported patient quality of life. The proportion of participants who were discharged as day surgery patients was higher in the local anaesthetic infiltration group than in the no local anaesthetic infiltration group (one trial; 97 participants; 33/50 (66.0%) in the local anaesthetic group versus 20/47 (42.6%) in the control group; RR 1.55; 95% CI 1.05 to 2.28; very low quality evidence). The effect of local anaesthetic on the length of hospital stay was compatible with a decrease, increase, or no diDereNce in the length of hospital stay between the two groups (four trials; 327 participants; MD -0.26 days; 95% CI -0.67 to 0.16; very low quality evidence). The pain scores as measured by the visual analogue scale (0 to 10 cm) were lower in the local anaesthetic infiltration group than the control group at 4 to 8 hours (13 trials; 806 participants; MD -1.33 cm on the VAS; 95% CI -1.54 to -1.12; very low quality evidence) and 9 to 24 hours (12 trials; 756 participants; MD -0.36 cm on the VAS; 95% CI -0.53 to -0.20; very low quality evidence). The effect of local anaesthetic on the time taken to return to normal activity between the two groups was imprecise and compatible with a decrease, increase, or no</p>	<p>Ahmad 1998, Beqiri 2012, Bilge 1997, Cantore 2008, Dath 1999, Feroci 2009, Hasan 2007, Hasaniya 2001, Lee 2001, Lepner 2003, Liang 2011, Liu 2009, Louizos 2005, Newcomb 2007, Nicolau 2008, Noma 2001, Paggiannopoulou 2003, Papziogas 2001, Pavlidis 2003, Rodriguez-Navarro 2011, Sara 1996, Shikano 1994, Sozbilen 2007, Ure 1993, Uzunkoy 2001, Zajackowska 2004.</p>

randomised clinical trials (irrespective of language, blinding, or publication status) comparing local anaesthetic wound infiltration versus placebo, no intervention, or inactive control during laparoscopic cholecystectomy, trials comparing different local anaesthetic agents for local anaesthetic wound infiltration, and trials comparing the different times of local anaesthetic wound infiltration were considered for the review.

Exclusion Criteria: not described / not meeting inclusion criteria.

difference in the time taken to return to normal activity (two trials; 195 participants; MD 0.14 days; 95% CI -0.59 to 0.87; very low quality evidence). None of the trials reported on return to work. 4 trials randomised a total of 149 participants to local anaesthetic wound infiltration prior to skin incision (74 participants) versus local anaesthetic wound infiltration at the end of surgery (75 participants). Two trials randomised a total of 176 participants to four different local anaesthetics (bupivacaine, levobupivacaine, ropivacaine, neosaxitoxin). Although there were differences between the groups in some outcomes the changes were not consistent. There was no evidence to support the preference of one local anaesthetic over another or to prefer administration of local anaesthetic at a specific time compared with another.

Author's Conclusion: Implications for practice: Serious adverse events were rare in studies evaluating local anaesthetic wound infiltration (very low quality evidence). There is very low quality evidence that infiltration reduces pain in low anaesthetic risk people undergoing elective laparoscopic cholecystectomy. However, the clinical importance of this reduction in pain is likely to be small.

**Methodical Notes**

Funding Sources: Internal sources  
 • None, Other.  
 External sources  
 • National Institute of Health Research, UK.

COI: None known.

Study Quality: Risk of bias in included studies One trial was at low risk of bias (Feroci 2009). All the remaining trials were at high risk of bias.

"The overall quality of evidence is low to very low. Although it is difficult to blind many interventions in surgery, this is one of the few interventions in which adequate blinding can be achieved and high quality evidence is possible. Nevertheless, this is the best evidence that is currently available."

Overall GRADE quality of evidence was considered to be very low or low.

Heterogeneity: We explored heterogeneity by the Chi2 test with significance set at a P value less than 0.10, and measured the quantity of heterogeneity by the I2 statistic (Higgins 2002). We also used overlapping of confidence intervals on the forest plot to determine heterogeneity.

Publication Bias: We used visual asymmetry on a funnel plot to explore reporting bias as more than 10 trials were identified. We performed the linear regression approach described by Egger 1997 to determine the funnel plot asymmetry. Selective reporting was also considered as evidence for reporting bias.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

All but one included studies were at high risk of bias; overall GRADE quality of evidence was considered to be very low or low, which limits the studies implications. This includes the high I-square and the lack of overlap of confidence intervals (downgraded by 2 points).

Marks, J. L. et al. Systematic review and metaanalysis of intraperitoneal instillation of local anesthetics for reduction of pain after gynecologic laparoscopy. J Minim Invasive Gynecol. 19. 545-53. 2012

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic review	Population: Women undergoing	Primary: Postoperative pain was measured in terms of a VAS score.	Barclay 1994, Chou 2005, El-

and meta-analysis (7 studies)  
To review the effect of intraperitoneal instillation of local anesthetics at laparoscopy on postoperative pain after laparoscopic surgery performed to treat benign gynecologic conditions.

Databases: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Ovid MEDLINE In-Process & Other Non-Indexed Citations.

Search period: 1979 - 09/2011

Inclusion Criteria: RCTs in which women undergoing laparoscopic surgery for treatment of benign gynecologic conditions were allocated to receive intraperitoneal analgesics or placebo/control intervention were selected. Intraperitoneal analgesia was defined as spraying or instillation of the analgesic solution into the peritoneal cavity at laparoscopy (either or after the actual procedure) or spreading analgesic gel over the operative site.

Exclusion Criteria: Studies that did not fit these criteria were excluded, as were trials that evaluated instillation of pain medication other than local analgesics and those involving procedures with the patient not under general anesthesia. Studies with the intraperitoneal analgesia group receiving co-interventions not administered to the control group were also excluded because an independent effect of intraperitoneal anesthesia could not be isolated.

laparoscopic surgery for treatment of benign gynecologic conditions.

Intervention: Intraperitoneal analgesics defined as spraying or instillation of the analgesic solution into the peritoneal cavity at laparoscopy (either or after the actual procedure) or spreading analgesic gel over the operative site

Comparison: Placebo/control intervention

Secondary: Postoperative nausea/vomiting, total analgesic requirements, and duration of hospital stay.

Results: Results: only summary results displayed here, rest see article.

The 7 included RCTs compared pain scores after administration of intraperitoneal analgesics or placebo/control during gynecologic laparoscopic surgery with benign indications. Outcome measures were pain scores (per visual analog scale) at 1 to 2, 4 to 6, and 24 hours postoperatively. Pain scores were significantly lower in the groups receiving local anesthesia at 1 to 2 hours (weighted mean difference [WMD], 21.82; 95% confidence interval [CI], 22.55 to 21.08) and 4 to 6 hours postoperatively (WMD, 22.00; 95% CI, 23.64 to 20.35), but were similar at 24 hours (WMD, 21.43; 95% CI, 21.15 to 0.96). Local analgesia instilled intraperitoneally significantly decreased pain during a 6-hour interval after gynecologic laparoscopy.

Author's Conclusion: Our metaanalysis suggests that intraperitoneal instillation of local analgesia is effective in reducing postoperative pain at 2 and 6 hours after gynecologic laparoscopic surgery. There does not seem to be any major adverse effects of the local anesthesia, such as nausea/vomiting.

Sherbiny 2009, Ezeh 1995, Helvacioğlu 1992, Shaw 2001, Wheatley 1994,

### Methodical Notes

**Funding Sources:** The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

**COI:** The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

**Study Quality:** The Cochrane risk of bias tool was used for risk assessment. Overall, it seems that the trials reported valid results.

**Heterogeneity:** A p value < .05 was required to determine statistically significant heterogeneity between trial results. A random effects model was used when there was significant heterogeneity between trial results (pain scores at 1–2 hours and 4–6 hours postoperatively), and a fixed effects model was used when there was no significant heterogeneity between trial results (pain scores at 24 hours).

**Publication Bias:** There are few studies reporting pain scores at 4 to 6 hours and 24 hours, and this prevents reliably commenting on the symmetry of estimates using funnel plots. However, the funnel plot for pain scores within the first 2 hours does not suggest the presence of a publication bias resulting in overestimation of treatment effect.

Notes:

High heterogeneity in some outcomes, likely due to differences in the comparison (control) of placebo, standard analgesia and combined analysis.

Marques, E. M. et al. Local anaesthetic infiltration for peri-operative pain control in total hip and knee replacement: systematic review and meta-analyses of short- and long-term effectiveness. *BMC Musculoskelet Disord.* **15.** 220. 2014

Evidence Types	level/Study	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (13 studies). To synthesise evidence from randomised controlled trials (RCTs) evaluating the effectiveness of peri-operative local anaesthetic infiltration for pain control in patients with THR and TKR.</p> <p>Databases: MEDLINE, Embase and Cochrane CENTRAL</p> <p>Search period: Inception - to 12 / 2012.</p> <p>Inclusion Criteria: RCTs of patients with primary unilateral THR or TKR receiving local anaesthetic infiltration before wound closure compared with patients receiving no local anaesthetic infiltration or placebo. We also included studies comparing local anaesthetic infiltration with other forms of analgesia and studies with additional post-wound closure delivery of analgesics through catheters and injections. No language restrictions were applied and translations were made by colleagues as required.</p> <p>Exclusion Criteria: Studies with interventions exclusively after wound closure and studies in patients receiving hip hemiarthroplasty or unicompartmental TKR.</p>	<p>Population: Patients with primary unilateral total hip replacement (THR) or total knee replacement (TKR).</p> <p>Intervention: Local anaesthetic infiltration (LIA).</p> <p>Comparison: No local anaesthetic infiltration or placebo</p>	<p>Primary: Pain at rest 24h, Pain at activity 24h, Pain at rest 48h, Pain at activity 48h,</p> <p>Secondary: length of hospital stay, mobilisation, opioid consumption, complications, long-term outcomes.</p> <p>Results: Results: only summary results displayed here due to length, rest see article. In 13 studies including 909 patients undergoing THR, patients receiving local anaesthetic infiltration experienced a greater reduction in pain at 24 hours at rest by standardised mean difference (SMD) -0.61 (95% CI -1.05, -0.16; p = 0.008) and by SMD -0.43 (95% CI -0.78 -0.09; p = 0.014) at 48 hours during activity. In TKR, diverse multi-modal regimens were reported. In 23 studies including 1439 patients undergoing TKR, local anaesthetic infiltration reduced pain on average by SMD -0.40 (95% CI -0.58, -0.22; p &lt; 0.001) at 24 hours at rest and by SMD -0.27 (95% CI -0.50, -0.05; p = 0.018) at 48 hours during activity, compared with patients receiving no infiltration or placebo. There was evidence of a larger reduction in studies delivering additional local anaesthetic after wound closure. There was no evidence of pain control additional to that provided by femoral nerve block. Patients receiving local anaesthetic infiltration spent on average an estimated 0.83 (95% CI 1.54, 0.12; p = 0.022) and 0.87 (95% CI 1.62, 0.11; p = 0.025) fewer days in hospital after THR and TKR respectively, had reduced opioid consumption, earlier mobilisation, and lower incidence of vomiting. Few studies reported long-term outcomes.</p> <p>Author's Conclusion: Our systematic review and meta-analysis shows that inclusion of local anaesthetic infiltration in a multimodal anaesthesia regimen is effective in reducing short-term pain and hospital stay in patients receiving THR and TKR. Enhanced pain control was observed when additional analgesia was provided after wound closure through a catheter but benefit should be weighed against a possible infection risk. For patients with TKR, inclusion of the non-steroidal anti-inflammatory agent ketorolac in the infiltrate seemed to enhance pain relief. There was no evidence of pain control additional to that provided by femoral nerve block in patients receiving TKR. Few studies reported long-term outcomes and future research should assess whether local anaesthetic infiltration can affect the development of long-term post-surgical pain.</p>	<p>Andersen 2010, Busch 2006, Carli 2010, Chen 2012, Essving 2010, Essving 2011, Fu 2006, Fu 2008, Han 2007, Koh 2012, Krenzel 2009, Mahadevan 2012, Meftah 2012, Ng 2012, Parvataneni 2007, Spreng 2007, Thorsell 2010, Toftdahl 2007, Vendittoli 2006, Zhang 2007.</p>	

#### Methodical Notes

**Funding Sources:** The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. This article outlines independent research commissioned by the National Institute for Health Research (NIHR) in England under its Programme Grants for Applied Research funding scheme (RP-PG-0407-10070). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

**COI:** The authors declare that they have no competing of interests.

**Study Quality:** Potential sources of bias were recorded in a Cochrane risk of bias table [14]. We considered random sequence generation, allocation concealment, blinding of participants and personnel, blind outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. We classified overall quality as low, unclear or high risk of bias.

**Heterogeneity:** We quantified the differences in treatment effects between groups using meta-regression. Heterogeneity within meta-analyses was quantified using the  $\tau^2$  and  $I^2$  statistics [26]. Sensitivity and sub-group analyses explored risk of bias in the study, use of additional analgesia delivered through a catheter or injection, and inclusion of non-steroidal inflammatory agents or steroids in the infiltrate.

No overall description of heterogeneity given, but it is very high for the main analyses of pain scores.

**Publication Bias:** "Inspection of funnel plots for each meta-analysis gave no strong indication of publication bias or small study effects, but numbers of studies in individual analysis groups were small such that it was difficult to assess asymmetry."

#### Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.

Publication bias investigated but not shown. High heterogeneity for pain outcomes, which limits implications. Some, but not

complete overlap with the newer meta-analysis from Sangleaur et al. (hip replacement). Quality of study investigated, but only reported in a supplement figure.

**Mungroop, T. H. et al. Preperitoneal or Subcutaneous Wound Catheters as Alternative for Epidural Analgesia in Abdominal Surgery: A Systematic Review and Meta-analysis. Ann Surg. 269. 252-260. 2019**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review and meta-analysis: (26 studies) To assess whether the location of wound catheters (ie, preperitoneal vs. subcutaneous) impacts outcomes, when compared with alternatives such as epidural analgesia. Databases: PubMed, Cochrane, and Embase databases.</p> <p>Search period: Inception - April 3, 2017.</p> <p>Inclusion Criteria: Studies were included in the systematic review if the following criteria were met: randomized controlled trials (RCTs) comparing continuous wound infiltration with an active comparator (epidurals or patient-controlled analgesia [PCA]) or sham analgesia (placebo/ saline) reporting on the primary endpoint.</p> <p>Exclusion Criteria: Studies were excluded for any of the following: articles in other languages than English, review articles, opinion papers, proceedings, editorials, studies on children, animal studies, articles not reporting on postoperatively outcomes, articles on <math>\leq 10</math> patients in both groups.</p>	<p>Population: Patients undergoing abdominal surgery.</p> <p>Intervention: Continuous wound infiltration with an active comparator (epidurals or patient-controlled analgesia [PCA])</p> <p>Comparison: Sham analgesia (placebo/ saline)</p>	<p>Primary: Pain in rest and while moving scored on a numeric rating scale (range: 0–10) at 24 hours postoperatively.</p> <p>Secondary: Pain scores at 12 and 48 hours postoperatively, opioid consumption (in IV-morphine equivalent), pain treatment related complications (wound infection, hematoma, and dehiscence), technical failure (placement failure, premature removal, leakage, or puncture failure), hospital stay (d), functional recovery, duration of ileus (passing first flatus, passing first stool, or bowel recovery [d]), satisfaction / patient reported outcomes (number of “excellent” satisfaction scores), urinary retention/ length of urinary catheter use, nausea and vomiting, and hypotension.</p> <p>Results: Study overview: 29 randomized controlled trials (RCTs) with 2059 patients were included. Methodological quality of these RCTs ranged from moderate to high. Results: only summary described due to length. In the one direct comparison (60 patients), preperitoneal catheters led to better pain control than subcutaneous catheters. Superiority of preperitoneal compared with subcutaneous placement was confirmed indirectly in placebo-controlled RCTs. Preperitoneal wound catheters provided comparable pain control compared with active controls, such as epidural analgesia. Recovery parameters, opioid consumption, incidence of hypotension, and patient satisfaction seemed to be in favor of preperitoneal wound catheters compared with active alternatives, as well as placebo.</p> <p>Author's Conclusion: This systematic review and meta-analysis shows that continuous wound infiltration is effective for pain management in abdominal surgery. Preperitoneal placement of wound catheters seems to be more effective than subcutaneous placement. Wound catheters are beneficial with respect to recovery with excellent patient satisfaction.</p>	<p>26 articles included, see article.</p>

**Methodical Notes**

**Funding Sources:** This research was funded in part by a grant from the Dutch Cancer Society (grant number UVA2013-5842).

**COI:** The authors report no conflicts of interest.

**Study Quality:** Two authors assessed the methodological quality of the included studies according to the Cochrane Collaboration tool. Studies were screened on selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other sources of bias, and were ranked with a low, high, or unclear risk of bias.

"Methodological quality of these RCTs ranged from moderate to high. "

**Heterogeneity:** I<sup>2</sup> was used to quantify heterogeneity and was graded as considerable when I<sup>2</sup> > 75%. Sensitivity analyses were performed to determine the influence of laparoscopic surgery and enhanced recovery protocols.

"Considerable heterogeneity was present in most comparisons, which may be caused by differences in procedures, incisions, and postoperative care."

**Publication Bias:** Publication bias not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

Downgrade to evidence level 2:

High heterogeneity was present in most analysis, which the author's are aware of. This is likely due to the differences in surgeries, but limits the analysis' implications for practice.

Publication bias not investigated.

No study descriptives or individual results for study quality.

**Ren, Y. et al. Efficacy of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia in abdominal**



Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis: 5 studies "To evaluate effects of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia in abdominal surgery." Databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.</p> <p>Search period: Inception - November 2018.</p> <p>Inclusion Criteria: (a) RCTs, (b) local wound infiltration was performed before or after operation, (c) adult patients (≥18 years old), (d) the experimental group included the comparison of DEX with local anaesthetics and local anaesthetics alone, at least,(e) abdominal operation, including minimally invasive surgery and open surgery, and (f) availability of full-text publication in English. The operation technique, the dosage of DEX, and the dosage and type of local anaesthetics were not considerations for inclusion.</p> <p>Exclusion Criteria: (a) were abstracts only, (b) were duplications, (c) had data loss, and (d) inaccurate statistical analysis was performed in the study.</p>	<p>Population: Patients undergoing abdominal operations (open and laparoscopic)</p> <p>Intervention: Dexmedetomidine (DEX) as an adjuvant to local wound infiltration anaesthesia.</p> <p>Comparison: local anaesthetics and local anaesthetics alone.</p>	<p>Primary: Postoperative pain (VAS score at 6, 12, 24h post-operative).</p> <p>Secondary: Total analgesic consumption 24h after surgery. Incidence of postoperative nausea and vomiting (PONV) 24h after surgery.</p> <p>Results: Results: <u>only summary results presented here, rest see article.</u> 5 randomised controlled trials (RCTs) involving 294 patients were included. Then, the outcome data were extracted from the studies and their effect sizes were calculated using Review Manager 5. As a result, the addition of DEX significantly reduced visual analogy scores at 6 hours after surgery (mean difference = -0.53[-0.82, -0.25], P &lt; .001), 12 hours after surgery (mean difference = -0.39 [-0.73, -0.05]; P = .03), and 24 hours after surgery (mean difference = -0.20 [-0.29, -0.11], P &lt; .001) and reduced total analgesic consumption within 24 hours after surgery (mean difference = -4.92 [-9.00, -0.84]; P = .02) compared with placebo groups. However, there was no difference in the incidence of postoperative nausea and vomiting (risk ratio = 0.68 [0.41, 1.14]; P = .14). In summary, DEX as a local anaesthetic adjuvant added for local wound infiltration anaesthesia in abdominal surgery could reduce visual analogy scores and postoperative analgesic consumption without changing incidence of postoperative nausea and vomiting.</p> <p>Author's Conclusion: "In conclusion, DEX as a local anaesthetic adjuvant added for local wound infiltration anaesthesia in abdominal surgery could reduce VAS scores and postoperative opioid consumption without changing the incidence of PONV. Meanwhile, more large-sample and high-quality RCTs are needed to increase the credibility identified in the current metaanalysis."</p>	<p>5 studies included: Hengfei Luan 2017, Jun-Ma Yu 2016, S.A. Mohamed 2018, Shaman Bhardwaj 2017, Swati Singh 2017.</p>

**Methodical Notes**

Funding Sources: "This study was supported by the National Natural Science Foundation of China (81800395) and Science and Technology Department of Henan Province (182102310159)  
National Natural Science Foundation of China, Grant/Award Number: 81800395; Science and Technology Department of Henan Province, Grant/Award Number: 182102310159"

COI: No conflicts of interest declared.

Study Quality: All the selected documents were reviewed by two reviewers to evaluate the methodological quality of the included RCTs independently, using the Cochrane Collaboration's risk of bias assessment tool. They evaluated the quality of each article from the random methods, the allocation of the hidden methods, the blind law of the research objects and the implementers, the blind method of the results measurement, the integrity of the result data, the selective report bias, and the other bias sources. Finally, the low-bias, high-bias, and unclear judgments were obtained. When they disagreed with each other, they discussed the disagreements to reach consensus or the issue was decided by two other reviewers.

Heterogeneity: The Q ( $\chi^2$ ) test and I2 statistics were used for assessing the studies' heterogeneity. If the P value for the Q test <.1 and I2 heterogeneity was considered not significant the fixed-effects model used otherwise we assumed that there random-effects to calculate effect size furthermore performed sensitivity analysis analyse sources of heterogeneity. p value for statistically>

Publication Bias: Pulication bias not investigated.

Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.  
 Publication bias not investigated. High heterogeneity in some of the results (PONV 24h)

Seanglelur, A. et al. The efficacy of local infiltration analgesia in the early postoperative period after total knee arthroplasty: A systematic review and meta-analysis. *Eur J Anaesthesiol.* 33. 816-831. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis: 28 studies.            Databases: Medline via PubMed and SCOPUS.</p> <p>Search period: Inceptions until 14th March 2013.</p> <p>Inclusion Criteria: Eligible studies were selected from all potential studies by two independent reviewers. The eligibility criteria were Population: adult patients who underwent primary unilateral or bilateral TKA; Intervention: intraoperative peri or intra-articular knee injection of analgesic drugs with or without postoperative intra-articular catheter placement; Comparator: no injection or placebo (for those with bilateral TKA, LIA was performed on one knee and no injection or placebo on the other); Outcomes: at least one of the following outcomes reported: pain intensity at-rest or at-activity measured at 24 or 48 h, opioid consumption during 0 to 24 and 24 to 48 h, mobilisation at 24 h, LOS, opioid side-effects (nausea and vomiting, rash or pruritus, respiratory depression and urinary retention), local anaesthetic toxicity and infection rate; Methodology: only RCTs published in English.</p> <p>Exclusion Criteria: Studies were excluded when data could not be extracted after we contacted authors or measured from the available reported graphs.</p>	<p>Population: Adult patients who underwent primary unilateral or bilateral total knee arthroplasty (TKA).</p> <p>Intervention: Intraoperative peri or intra-articular knee injection of analgesic drugs with or without postoperative intra-articular catheter placement;</p> <p>Comparison: no injection or placebo (for those with bilateral TKA, Local infiltration analgesia (LIA) was performed on one knee and no injection or placebo on the other).</p>	<p>Primary: Pain intensity at-rest or at-activity measured at 24 or 48 h,</p> <p>Secondary: Opioid consumption during 0 to 24 and 24 to 48 h, mobilisation at 24 h, LOS, opioid side-effects (nausea and vomiting, rash or pruritus, respiratory depression and urinary retention), local anaesthetic toxicity and infection rate;</p> <p>Results: Results: only summary results displayed here, for the rest see article.</p> <p>In total 38 RCTs were included. LIA groups had lower pain scores, opioid consumption and postoperative nausea and vomiting, higher range of motion at 24 h and shorter LOS than no injection or placebo. After subgroup analysis, intraoperative peri-articular but not intra-articular injection had lower pain score at 24 h than no injection or placebo with the pooled mean difference of pain score at rest of -0.89 [95% CI (-1.40 to -0.38); I<sup>2</sup> = 92.0%]. Continuing with postoperative injection or infusion reduced 24-h pain score with the pooled mean difference at rest of -1.50 [95% CI (-1.92 to -1.08); I<sup>2</sup> = 60.5%]. There was no additional benefit in terms of pain relief during activity, opioid consumption, range of movement or LOS when LIA was used as an adjunct to regional anaesthesia. Four out of 735 patients receiving LIA reported deep knee infection, three of whom had had postoperative catheter placement.</p> <p>Author's Conclusion: "LIA is effective for acute pain relief, and is associated with a reduction in postoperative nausea vomiting and hospital stay, and improvement of range of movement after TKA. Peri-articular injection reduces pain within 24 h, whereas intra-articular injection does not. When catheter placement for postoperative injection or infusion is used, the analgesic effects can be extended to 48 h, but the risk of catheter-related infection is uncertain. The efficacy of LIA as an adjunct to regional anaesthetic techniques is not demonstrated."</p>	<p>28 studies included.            Vendittoli 2006,            Andersen 2008,            Essving 2010, Kazak Bengisum 2010, Zhang 2011, Mauerhan 1997, Klasen 199, Tanaka 2001, Browne 2004, Garcia 2010, Rosen 2010, Fajardo 2011, Guara sobrinho 2012, Nakai 2013, Shen 2015, Busch 2006, Fu 2009, Fu 2010, Zhang 2011, Chen 2012, Lamplot 2013, Nakai 2013, Leownorasate 2014, Niemelainen 2014, Milani 2015, Ong Jc 2010, Ikeuchi 2012.</p>

**Methodical Notes**

Funding Sources: None.

COI: None.

**Study Quality:** Risk of bias was independently assessed in duplicate by five reviewers, using 'Cochrane Collaboration's tool for assessing risk of bias'. Any disagreement was resolved by discussion among the reviewers.

"26 (68.4%) and 22 (57.9%) studies properly reported random sequence generation and allocation concealment respectively. Two-third of studies (n=25 studies) had adequately blinded both patients and outcome assessors. Outcome assessments were also mostly well defined in 31 studies (81.6%), and the risk of selective reporting bias was very low."

**Heterogeneity:** "Heterogeneity was assessed using Cochrane's Q test and I2 statistics. A random effects model was used for pooling when heterogeneity was present (i.e. P value<0.1 or I2 ≥ 25%); otherwise, a fixed effect model was applied."

Very high heterogeneity in all analyses. "Although sources of heterogeneity were explored by sensitivity and subgroup analysis of several possible causes, heterogeneity in some outcomes still exists. This could be explained by various drugs and doses of LIA, volume of injection, administration sites which were quite operator dependent and different analgesic adjuncts."

**Publication Bias:** "Publication bias was assessed by Funnel plot and Egger test. Either the asymmetric funnel plot or the significant Egger P value (P0.05) determined the use of contour-enhanced funnel plot."

"Funnel plots were constructed for 24-h VAS for pain at rest between LIA versus no injection or placebo when LIA was used as a primary treatment or an adjunct to regional analgesia. Both plots showed asymmetry, but Egger tests were not statistically significant with P value 0.75 and 0.28"

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

High heterogeneity which limits the implications from this research (f.e I<sup>2</sup> = 90.7% for main analysis 24h VAS). The authors are aware of this problem" Although sources of heterogeneity were explored by sensitivity and subgroup analysis of several possible causes, heterogeneity in some outcomes still exists. This could be explained by various drugs and doses of LIA, volume of injection, administration sites which were quite operator dependent and different analgesic adjuncts."

**Tam, K. W. et al. Effect of wound infiltration with ropivacaine or bupivacaine analgesia in breast cancer surgery: A meta-analysis of randomized controlled trials. Int J Surg. 22. 79-85. 2015**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review and meta-analysis: 13 studies</p> <p>A systematic review of randomized controlled trials to evaluate the efficacy of bupivacaine or ropivacaine analgesia for pain relief in breast cancer surgery.</p> <p>Databases: PubMed, Embase, the Cochrane Library, Scopus, and the ClinicalTrials.gov registry.</p> <p>Search period: Inception - July 2015.</p> <p>Inclusion Criteria: RCTs evaluating the outcome of wound infiltration with local analgesics in breast cancer surgery. In addition, studies had to clearly report the inclusion and exclusion criteria for patients, the anesthetic technique, the surgical technique used to treat breast cancer, and the definition and evaluation of postoperative pain.</p> <p>Exclusion Criteria: (1) the patients had not received partial or modified radical mastectomy for breast cancer, such as in studies that only included breast tumor sampling; (2) the patients had undergone non-cancer-related breast surgery; (3) the clinical outcomes had not been clearly stated; or (4) duplicate reporting of patient cohorts had occurred.</p>	<p>Population: Patients undergoing partial or modified radical mastectomy for breast cancer.</p> <p>Intervention: Wound infiltration using Bupivacaine or Ropivacaine analgesia. Described as experimental drug infiltration.</p> <p>Comparison: Control group: (not described)</p>	<p>Primary: Postoperative pain scores at 1, 2, 12 and 24 hours.</p> <p>Secondary: Postoperative pain: postoperative vs. preemptive local infiltration. Complication</p> <p>Results: Results: Only summary results displayed here due to length, rest see full article. We reviewed 13 trials with 1150 patients. We found no difference in postoperative pain reduction at 1, 12, and 24 h after breast cancer surgery between the experimental and control groups. The severity of pain was significantly reduced in the experimental group (weighted mean difference -0.19; 95% confidence interval: -0.39 -0.00) at 2 h postoperatively. Moreover, postoperative analgesic consumption did not differ significantly between the groups. No major drug-related complication was observed in any study.</p> <p>Author's Conclusion: The results of our meta-analysis revealed that the infusion of ropivacaine or bupivacaine following breast cancer surgery decreased immediate postoperative pain but did not reduce pain at 12, and 24 h postoperatively. Although some trials showed that wound infiltration with ropivacaine or bupivacaine reduced immediate postoperative pain, the analgesic consumption did not differ between the groups. According to the results of this meta-analysis, the potential clinical value of local anesthetic infiltration for postoperative pain relief can be questioned.</p>	<p>13. articles included: Albi-Feldzer 2013, Baudry 2008, Campbell 2014, Johansson 2003, Johansson 2000, Jonnavithula 2015, Mohamed 2013, Petersson 2001, Rica 2007, Talbot 2004, Vallejo 2006, Vigneau 2011, Zielinski 2011.</p>

**Methodical Notes**

**Funding Sources:** The authors Ka-Wai Tam, Shin-Yan Chen, Tsai-Wei Huang, Chao- Chun Lin, Chih-Ming Su, Ching-Li Li, Yuan-Soon Ho, Wan-Yu Wang, and Chih-Hsiung Wu have no financial ties to disclose.

**COI:** All authors have no conflicts of interest or financial ties to disclose.

**Study Quality:** Two reviewers independently assessed the methodological quality of each study. The quality of the studies was assessed using the “risk of bias” method recommended by the Cochrane Collaboration. Several domains were assessed, such as the adequacy of randomization, allocation concealment, blinding of the patients and outcome assessors, length of follow-up, information provided on study withdrawals and whether intention-to-treat (ITT) analysis was performed, and freedom from other biases.

**Heterogeneity:** Cochrane Q tests and I2 statistics were used to evaluate the statistical heterogeneity and inconsistency of treatment effects among the studies, respectively. Statistical significance was set at  $P < 0.1$  for the Cochrane Q tests. Statistical heterogeneity was assessed by performing the I2 test, with I2 quantifying the proportion of the total outcome variability that was attributable to variability among the studies. Sensitivity analyses were performed to assess any impact of the study quality on the effect estimates. Subgroup analyses were also performed by pooling estimates for similar patient subsets among trials, where available.

**Publication Bias:** Not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

Downgrade to evidence level 2.

No definition or inclusion criterion for control group available, which could be causing heterogeneity (standard, administration dosage etc). In addition Bupivacaine and Ropivacaine were analyzed together. Despite this the heterogeneity is surprisingly low. No investigation of publication bias.

Tong, Y. S. et al. Effect of extraperitoneal bupivacaine analgesia in laparoscopic inguinal hernia repair: a meta-analysis of randomized controlled trials. *Hernia*. 18. 177-83. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level: 1</b></p> <p><b>Study type:</b> Systematic review and meta-analysis (8 studies) To evaluate the efficacy of extraperitoneal bupivacaine treatment during laparoscopic inguinal hernia repair for the reduction of postoperative pain.</p> <p><b>Databases:</b> PubMed, EMBASE, Scopus, and Cochrane central registers of controlled trial databases, as well as the ClinicalTrials.gov registry (<a href="http://clinicaltrials.gov/">http://clinicaltrials.gov/</a>)</p> <p><b>Search period:</b> Inception - October 2012.</p> <p><b>Inclusion Criteria:</b> RCTs that evaluated the outcome of extraperitoneal bupivacaine analgesia in laparoscopic TEP inguinal hernia repair. Studies were required to clearly report the inclusion and exclusion criteria for patients, the anesthetic technique, the surgical technique of TEP hernioplasty, the definition and evaluation of postoperative pain, and the use of appropriate study controls.</p> <p><b>Exclusion Criteria:</b> Previous RCTs were excluded from our metaanalysis based on the following criteria: (1) patients underwent other surgical procedures concomitantly, such as TAPP and non-mesh repairs; (2) patients were younger than 18 years; (3) the appropriate data could not be extracted or calculated from the published results; or (4) duplicate reporting of patient cohorts had occurred.</p>	<p><b>Population:</b> Patients undergoing laparoscopic total extraperitoneal (TEP) inguinal hernioplasty.</p> <p><b>Intervention:</b> Extraperitoneal bupivacaine analgesia</p> <p><b>Comparison:</b> Control, not specified.</p>	<p><b>Primary:</b> Occurrence and the severity of postoperative pain at 2, 4, 6, 8 and 12 h.</p> <p><b>Secondary:</b> Complications and analgesia consumption.</p> <p><b>Results:</b> Results: Only summar results displayed here due to length. We reviewed 8 trials that included a total of 373 patients. We found no difference between the groups in postoperative pain reduction following laparoscopic TEP inguinal hernia repair. The intensity of pain was not significantly different between the bupivacaine treatment group and the control group. The pooled mean differences in pain scores were -0.26 (95 % CI -0.72 to 0.21) at 4–6 h and -0.47 (95 % CI -1.24 to 0.29) at 24 h. No bupivacaine-related complications were reported.</p> <p><b>Author's Conclusion:</b> In conclusion, the results of our meta-analysis revealed that extraperitoneal instillation of bupivacaine following TEP inguinal hernioplasty did not show a greater reduction in postoperative pain than the placebo treatments. Based on these results, we cannot recommend extraperitoneal bupivacaine analgesia during laparoscopic TEP inguinal hernia repair for routine practice.</p>	<p>Abbas 2010, Bar-Dayyan 2004, Hon 2009, Kumar 2009, O'Riordain 1998, Saff 1998, Subwongcharoenet 2010, Suvikapakornkulet 2009,</p>

**Methodical Notes**

**Funding Sources:** The authors have no conflict of interest or financial ties to disclose.

**COI:** The authors have no conflict of interest or financial ties to disclose.

**Study Quality:** We assessed the methodological quality of each study based on the adequacy of the randomization, the allocation concealment, the blinding of the patients and the outcome assessors, the length of the follow-up period, the reporting of study withdrawals, and the performance of an intention-to-treat analysis. 6 studies used acceptable methods of randomization, and 5 studies clearly described the method of allocation concealment. All studies reported the blinding of the patients and the outcome assessors, except for one. All studies performed an intention-to-treat analysis. No patients withdrew during the follow-up periods of the selected studies.

**Heterogeneity:** To evaluate the statistical heterogeneity and the inconsistency of treatment effects across the studies, the Cochrane Q test and I<sup>2</sup> statistics were used, respectively. Statistical significance was set at 0.10 for the Cochrane Q tests. The proportion of the total outcome variability that was attributable to the variability across the studies was quantified as I<sup>2</sup>.

**Publication Bias:** Publication bias not investigated, but not feasible below 10 studies.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

Unclear or lacking definition of the comparison (controls). Which may explain the high heterogeneity in one of the main outcomes (postoperative pain score at 24 hours I<sup>2</sup>=82%).

Ventham, N. T. et al. Evaluation of novel local anesthetic wound infiltration techniques for postoperative pain following colorectal resection surgery: a meta-analysis. *Dis Colon Rectum*. 57. 237-50. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level: 1</b></p> <p><b>Study type:</b> Systematic review and meta-analysis (12 studies). This study aims to evaluate the efficacy of novel local anesthetic techniques in colorectal surgery. <b>Databases:</b> Electronic literature search of PubMed, EMBASE, and Cochrane databases.</p> <p><b>Search period:</b> 01/1990 to 02/2013)</p> <p><b>Inclusion Criteria:</b> The study inclusion criteria were as follows: randomized controlled trials in adult humans (&gt;16 years) undergoing open or laparoscopic colonic or rectal resection (including hemicolectomy, colectomy, anterior resection, abdominoperineal resection) for neoplastic or benign disease.</p> <p><b>Exclusion Criteria:</b> nonrandomized trials, children &lt;16 years, pharmacodynamics/kinetic studies, and irrelevant techniques. Included interventions included TA P block, intraperitoneal LA instillation, and LA infiltration by wound catheters. Excluded interventions include subcutaneous LA infiltration, infiltration of drug other than local anesthetic (eg, nonsteroidal anti-inflammatory drug), neuraxial analgesia, and intravenous LA. The comparator group was defined as placebo/routine analgesia.</p>	<p><b>Population:</b> Adult humans (&gt;16 years) undergoing open or laparoscopic colonic or rectal resection (including hemicolectomy, colectomy, anterior resection, abdominoperineal resection) for neoplastic or benign disease.</p> <p><b>Intervention:</b> Novel local anesthetic wound infiltration techniques such as wound catheter, transversus abdominis plane block, and intraperitoneal instillation in colorectal surgical procedures.</p> <p><b>Comparison:</b> Placebo/routine analgesia.</p>	<p><b>Primary:</b> Opiate requirement at 24 hours.</p> <p><b>Secondary:</b> Opiate requirements at 48 hours, pain numerical rating score at 24 and 48 hours at rest and on movement, recovery (length of stay, nausea and vomiting, time until bowel movement and diet resumption), and complications. Subgroup analysis was performed to evaluate specific local anesthetic techniques and open and laparoscopic surgery.</p> <p><b>Results:</b> Results: only summary results displayed due to length. 12 randomized controlled trials compared local anesthetic techniques with placebo/routine analgesia. Primary outcome not significant. Local anesthetic techniques demonstrated a significant reduction in opiate requirement at 48 hours (7 trials, 622 patients, I<sup>2</sup> = 80%; WMD -15.5mg, -25.3 to -5.6; p = 0.002). Local anesthetic techniques were also associated with lower pain scores on movement at 24 (7 studies, 637 patients, I<sup>2</sup> = 91%; WMD -1.1, -2 to 0.2; p = 0.02) and 48 hours ((5 studies, 537 patients, I<sup>2</sup> = 47%, WMD -0.7, -1.2 to -0.2; p = 0.004), shorter length of stay (9 studies, 755 patients, I<sup>2</sup> = 0%; WMD -0.6, -1.1 to 0.1; p = 0.02), and earlier resumption of diet (3 studies, 150 patients, I<sup>2</sup> = 36%; WMD -0.5 days, -1 to 0.04; p = 0.03).</p> <p><b>Author's Conclusion:</b> This meta-analysis suggests that novel LA blocks are more efficacious than placebo with routine analgesia, and may be usefully integrated as part of a multimodal enhanced recovery program in colorectal surgery. Wound catheters provide effective analgesia for 48 hours, and, although single- administration LA techniques appear effective for the first 24 hours, data beyond 24 hours are lacking.</p>	<p>12 studies included: Baig 2006, Beaussier 2007, Bharti 2011, Cheong 2011, Kahokehr 2011, McConnell 2017, Moore 2012, Ozturk 2011, Park 2011, Polglase 2007, Walter 2013, Wang 2010.</p>

**Methodical Notes**

**Funding Sources:** None reported.

**COI:** not declared.

**Study Quality:** 2 authors independently assessed the quality and potential bias of each paper by using a modified 15-point score adapted from criteria used by Chalmers, Jadad, and colleague.

**Heterogeneity:** A random effect DerSimonian-Laird model was chosen to provide the most conservative effects estimate. Results were presented with 95% CIs and heterogeneity was assessed by using  $t^2$ ,  $\chi^2$ , and  $I^2$ . Heterogeneity was considered significant if  $p < 0.1$  and classified as low ( $I^2 < 50\%$ ), moderate ( $I^2 51\%–75\%$ ), and high ( $I^2 > 75\%$ ).

**Publication Bias:** not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis

High heterogeneity in the significant outcomes for several outcomes: opiate requirement at 48 hours ( $I^2 = 80\%$ ); pain scores on movement at 24 ( $I^2 = 91\%$ ); 48 hours ( $I^2 = 47\%$ ). This is likely caused by the comparison being control analgesia as well as placebo and the differences in dose. This limits the implications of these results.

Publication bias not investigated.

**Wang, J. et al. The Effect of Local Anesthetic Infiltration Around Nephrostomy Tract on Postoperative Pain Control after Percutaneous Nephrolithotomy: A Systematic Review and Meta-Analysis. Urol Int. 97. 125-33. 2016**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review and meta-analysis (6 studies)</p> <p>To assess the safety and efficacy of local anesthetic infiltration around nephrostomy tract on postoperative pain control after percutaneous nephrolithotomy.</p> <p>Databases: Embase, PubMed, Medline, and Cochrane Library</p> <p>Search period: January 2001 to December 2015.</p> <p>Inclusion Criteria: (1) randomized controlled trials (RCTs); (2) patients must undergo PCNL, except tubeless PCNL; (3) the study described at least one outcome of the following: hemoglobin (Hb) alteration, analgesic demand time, total analgesic dose, hospital stay, Visual Analog Scale (VAS) at 6th hour after PCNL (VAS score-6 h), VAS score-24 h; (4) the data from included studies could be used in the meta-analysis directly or could be converted to statistical formula ; (5) local anesthetic infiltration around nephrostomy tract must be as an intervention compared with placebo (saline) or a control group.</p> <p>Exclusion Criteria: (1) repeated reports; (2) non-RCTs; (3) the data from included studies were not in the appropriate format or could not be obtained from the authors; (3) the full text of the study could not be obtained.</p>	<p>Population: Patients must undergo Percutaneous nephrolithotomy (PCNL), except tubeless PCNL.</p> <p>Intervention: Local anesthetic infiltration around nephrostomy tract.</p> <p>Comparison: Placebo (saline) or a control group.</p>	<p>Primary: Analgesia requirement, time of First Analgesic Demand (h), Visual Analog Scale (VAS) at 6th hour after PCNL (VAS score-6 h), VAS score-24 h</p> <p>Secondary: Hemoglobin (Hb) alteration, Operation time, hospital stay.</p> <p>Results: Study overview: 6 RCTs identified. They were published in English from 2001 to 2015. Of the 6 articles, 3 were from Turkey, one from India, one from Thailand and one from Canada. The samples size of these trials was in the range 34–105. There were no statistically meaningful differences found for number, age, sex, or stone burden and location.</p> <p>Results: Only summary due to length, rest see article. "Our results showed that the consumption of analgesic was less in the experimental group than in the control group (WMD <math>-25.32</math>, 95% CI <math>-48.09</math> to <math>-2.55</math>, <math>p = 0.003</math>). There was no significant difference between the mean Visual Analog Scale (VAS) in the experimental group than the control group after 6 h while significantly lower after 24 h. The time of first analgesic demand was significantly longer in the experimental group (WMD <math>2.19</math>, 95% CI <math>0.98– 3.41</math>). There was no significant difference between 2 groups in terms of operation time, hemoglobin (Hb) alteration, and hospital stay."</p> <p>Author's Conclusion: Our study indicated that local anesthetic infiltration around the nephrostomy tract had similar efficacy to the control group (no local anesthetic infiltration group) in terms of operation time, Hb alteration, and hospital stay, but offers some potential advantages over the control group (no local anesthetic infiltration group) in terms of analgesia requirement, the time of first analgesic demand, and VAS-24 (VAS score at 24th hour after the procedure). We believe that local anesthetic infiltration around the nephrostomy tract may prove a better alternative for postoperative pain management. However, good quality and large studies with long-term follow-up are warranted for further research.</p>	<p>6 articles: Tüzel 2014, Ugras 2007, Kirac 2013, Jonnavithula 2009, Honey 2013, Lojanpiwat 2015.</p>

**Methodical Notes**

Funding Sources: None.

COI: None.

**Study Quality:** Risk of bias was evaluated independently by 2 reviewers and arguments regarding methodology quality were resolved with a majority vote by 3 reviewers. The risk of bias of each trial included assessed by the Cochrane handbook for systematic reviews of interventions.

No reporting of individual risk of bias for each study or overall results. Visual inspection of the graph reveals risk of bias was considered to be low in the majority of studies, as well domains.

**Heterogeneity:** The data were analyzed using the randomeffects model because of clinical differences among the studies included (e.g. type of analgesic, inclusion, different anaesthetic, and so on). The Q (chi-square test) and I<sup>2</sup> statistics were used to assess heterogeneity. All of the tests were two-sided and p < 0.05 was thought to be statistically significant.

**Publication Bias:** Not investigated, which is adressed in the discussion "Third, publication bias should also not be ignored because small studies with null results tend not to be published." But with n<10 no statistic investigation is feasible.

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

Downgrade to level 2:

High heterogeneity I<sup>2</sup> ≥ 84 for 3 of the main outcomes (analgesia requirement, analgesic demand, VAS score-6 h). This is likely due to the fact that the intervention included different substances (ropivacaine, bupivacaine, levobupivacaine). In addition comparison also included studies with placebo infiltration as well as no infiltration. This is not adressed in the discussion and no sensitivity analysis or subgroup has been performed.

Inclusion criteria were not stringent, which led to the inclusion of several studies with different interventions and comparisons, which were all analyzed together.

No available results for individual study quality.

Yong, L. et al. Intraperitoneal ropivacaine instillation versus no intraperitoneal ropivacaine instillation for laparoscopic cholecystectomy: A systematic review and meta-analysis. *Int J Surg.* **44.** 229-243. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (12 studies). To assess the benefits and disadvantage of intraperitoneal instillation of ropivacaine in people undergoing laparoscopic cholecystectomy.</p> <p>Databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Science Citation Index Expanded.</p> <p>Search period: Inception - December 2016.</p> <p>Inclusion Criteria: All randomized trials. People undergoing laparoscopic cholecystectomy irrespective of age, elective or emergency surgery. Only trials comparing intraperitoneal instillation of ropivacaine (irrespective of timing of delivery, and the method of delivery) with no intraperitoneal instillation of ropivacaine can be concluded. We accepted any of the following control groups: normal saline, another placebo, or no instillation of any drug or fluid. Co-interventions were allowed if carried out equally in the trial groups.</p> <p>Exclusion Criteria: none</p>	<p>Population: People undergoing laparoscopic cholecystectomy irrespective of age, elective or emergency surgery</p> <p>Intervention: Intraperitoneal instillation of ropivacaine (irrespective of timing of delivery, and the method of delivery)</p> <p>Comparison: No intraperitoneal instillation of ropivacaine.</p>	<p>Primary: 1. Pain (overall pain) at different time points (4e8 h and 9e24 h). Only studies reporting pain scores on a visual analogue scale (VAS) (0e100 mm or 0e10 cm) were included.</p> <p>2. Adverse events Adverse events defined as any event that was life-threatening, jeopardised the person or required intervention to prevent it. We classified complications such as bile duct injury; bile leaks; reoperations; intra-abdominal collections; convulsions; wound infections, vomiting as adverse events.</p> <p>Secondary: 1. The Post-anesthesia care unit (PACU) stay time.</p> <p>Results: Sutdy overview: 12 suitable studies were identified. A total of 853 participants were randomised to intraperitoneal ropivacaine instillation (442 participants) versus "no intraperitoneal ropivacaine instillation" (411 participants). Results: only summary results displayed here, rest see article. The pain scores as measured by the visual analogue scale (VAS) were significantly lower in the ropivacaine instillation group than the control group at 4e8 h (10 trials; 751 participants; MD -0.64 cm; 95% CI -0.86 to -0.43; p &lt; 0.00001) and at 9e24 h (9 trials; 582 participants; MD -0.47 cm; 95% CI -0.66 to -0.28; p &lt; 0.00001). The proportion of people who developed the adverse events were less in the ropivacaine instillation group than the control group (RR 0.60; 95% CI 0.45 to 0.79; p = 0.0002). There was no significant difference in the Post-anesthesia care unit (PACU) stay time between the two groups (3 trials; 197 participants; MD -3.77 min; 95% CI -10.24 to 2.69). The overall quality of evidence was very low.</p> <p>Author's Conclusion: A review by Kahokehr et al. concluded that intraperitoneal local anaesthetic instillation reduced pain and no further trials were necessary. Another review reported that intraperitoneal instillation of local anaesthetic resulted in a reduction of the mean pain score. Our conclusions are similar in some aspects to some of the above reviews in that we have found that the rate of adverse events in studies of</p>	<p>Abet 2016, Bhatia 2014, Fassoulaki 2016, Fu 2009, Igelmo 2013, Kim 2010, Kucuk 2007, Labaille 2002, Llu 2015, Maestroni 2002, Nicolau 2008, Niknam 2014.</p>

ropivacaine intraperitoneal instillation are low and reduces pain in people undergoing laparoscopic cholecystectomy. However, we have concluded that more trials are need to investigate the clinical impact. Improvement of postoperative pain management offers great benefit to patient care and quality of life. The strengths of our study are that it is very relevant to the Enhanced Recovery After Surgery (ERAS). It provides surgeons and anaesthesiologists with further opportunity to improve patient comfort.

#### Methodical Notes

**Funding Sources:** No sources of support supplied.

**COI:** No potential conflicts of interest were disclosed.

**Study Quality:** We independently assessed the risk of bias in the trials without masking the trial names. We followed the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions.  
"The overall quality of evidence was very low."

**Heterogeneity:** We explored heterogeneity by the Chi [2] test, with significance set at a P value of 0.10, and measured the quantity of heterogeneity by the I2 statistic. A significant heterogeneity presents when I2 > 50%.  
Heterogeneity was only significant in subgroup analyses.

**Publication Bias:** We planned to use a funnel plot to explore bias in the presence of at least 10 trials for the specific outcome.

We explored reporting bias only for pain at four to 8 h by funnel plots because of the presence of adequate number of trials for this outcome only. The funnel plots in the presence of reporting bias. The Egger's test revealed report bias (P value = 0.001).

**Notes:**

Oxford level of evidence: 1 Systematic review and meta-analysis.

The overall quality of evidence was considered to be very low by the authors which limits implications of the article.



Literatursammlung:

Phantomschmerz

Inhalt: 3 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Alviar, M. J. 2016	1	SR (14 studies, one new in this update)
Johnson, M. I. 2015	1	SR (no study included)
Weinstein, E. J. 2018	1	SR and META (63 studies in total - 3 regarding limb amputation)

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 3 Bewertung(en)

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Alviar, M. J. et al. Pharmacologic interventions for treating phantom limb pain. Cochrane Database Syst Rev. 10. CD006380. 2016</p> <p>Evidence level: 1</p> <p>Study type: SR (14 studies, one new in this update)</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, and Embase, clinical trials databases and reference lists of retrieved papers.</p> <p>Search period: Original search September 2011 and current update in April 2016.</p> <p>Inclusion Criteria: RCTs, qRCTs</p> <p>Exclusion Criteria: Studies with sample sizes of 5 or less; short abstracts from conferences or meetings with inadequate or</p>	<p>Population: Patients with established phantom limb pain (PLP).</p> <p>Intervention: Pharmacologic agents given singly or in combination, in any dose, by any route were eligible. Preoperative, pre-emptive, intraoperative, and perioperative pharmacologic interventions undertaken to prevent PLP were not eligible.</p> <p>Comparison: placebo, another active treatment, or no treatment.</p>	<p>Primary: Change in pain intensity.</p> <p>Secondary: Function, sleep, depression or mood, quality of life, adverse events, treatment satisfaction, and withdrawals from the study. We considered short-term (less than or equal to 3 months) and long-term (more than 3 months) outcomes.</p> <p>Results: 269 patients were included.</p> <p>Classes of drugs: botulinum neurotoxins (BoNT/A), NMDA receptor antagonists, opioids, anticonvulsants, antidepressants, calcitonins, and local anaesthetics.</p> <p>Botulinum neurotoxins (new in this review!) BoNT/A did not improve phantom limb pain intensity during the six months of follow-up compared with lidocaine/methylprednisolone.</p> <p>Opioids: Compared with placebo, morphine (oral and intravenous) was effective in decreasing pain intensity in the short term with reported adverse events being constipation, sedation, tiredness, dizziness, sweating, voiding difficulty, vertigo, itching, and respiratory problems.</p> <p>NMDA: The N-methyl D-aspartate (NMDA) receptor antagonists ketamine (versus placebo; versus calcitonin) and dextromethorphan (versus placebo), but not memantine, had analgesic effects. The adverse events of ketamine were more serious than placebo and calcitonin and included loss of consciousness, sedation, hallucinations, hearing and position impairment, and insobriety.</p> <p>Anticonvulsants: The results for gabapentin in terms of pain relief were conflicting, but combining the results favoured treatment group (gabapentin) over control group (placebo) (mean difference -1.16, 95% confidence interval -1.94 to -0.38; 2 studies). However, gabapentin did not improve function, depression score, or sleep quality. Adverse events experienced were somnolence, dizziness, headache, and nausea.</p> <p>Antidepressants: Compared with an active control benzotropine mesylate, amitriptyline was not effective in PLP, with dry mouth and dizziness as the most frequent adverse events based on one study.</p> <p>Calcitonins: The findings for calcitonin (versus placebo; versus ketamine) and local anaesthetics (versus placebo) were variable. Adverse events of calcitonin were headache, vertigo, drowsiness, nausea, vomiting, and hot and cold flushes.</p> <p>Most of the studies were limited by their small sample sizes.</p>	<p>Abraham 2003; Bone 2002; Casale 2009; Eichenberger 2008; Huse 2001; Jaeger 1992; Maier 2003; Nikolajsen 1996; Robinson 2004; Schwenkreis 2003; Smith 2005; Wiech 2004; Wu 2002; Wu 2012.</p>

no reporting of data; studies in which participants had stump pain or residual limb pain alone, or postamputation pain that was not phantom pain, or where phantom pain was mixed with other neuropathic pains; studies where participants with phantom pain were mixed with participants with other postamputation pains if no separate or subgroup analyses were reported for phantom pain.

**Author's Conclusion:** Since the last version of this review, we identified another study that added another form of medical therapy, BoNTs, specifically BoNT/ A, to the list of pharmacologic interventions being reviewed for clinical efficacy in phantom limb pain. However, the results of this study did not substantially change the main conclusions. The short- and long-term effectiveness of BoNT/A, opioids, NMDA receptor antagonists, anticonvulsants, antidepressants, calcitonins, and local anaesthetics for clinically relevant outcomes including pain, function, mood, sleep, quality of life, treatment satisfaction, and adverse events remain unclear. Based on a small study, BoNT/A (versus lidocaine/methylprednisolone) does not decrease phantom limb pain. Morphine, gabapentin, and ketamine demonstrate favourable short-term analgesic efficacy compared with placebo. Memantine and amitriptyline may not be effective for PLP. However, results must be interpreted with caution, as they were based mostly on a small number of studies with limited sample sizes that varied considerably and also lacked long-term efficacy and safety outcomes. The direction of efficacy of calcitonin, local anaesthetics, and dextromethorphan needs further clarification. Overall, the efficacy evidence for the reviewed medications is thus far inconclusive. Larger and more rigorous randomised controlled trials are needed for us to reach more definitive conclusions about which medications would be useful for clinical practice.

**Methodical Notes**

**Funding Sources:** Cochrane Review Group funding acknowledgement: the National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. **Disclaimer:** the views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health.

**COI:** MJA: none known. MJA is a Rehabilitation Medicine specialist and has completed PhD Research in Orthopaedic Rehabilitation. TAH: none known. TAH is a Rehabilitation physician and manages patients with amputations and complications including phantom limb pain. MD: none known. MD is a Rehabilitation Medicine specialist and manages both adult and paediatric patients with musculoskeletal and neurologic conditions including patients with neuropathic pain.

**Study Quality:** Risk of bias for each included study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Sequence generation, blinding of outcome assessment, and completeness of outcome data were most often inadequately reported. Another important source of bias in the review was the small size of studies. Overall, we considered 10 studies to be at low risk of bias and 4 to be at unclear risk of bias.

**Heterogeneity:** The amount of statistical heterogeneity among the studies by computing the I<sup>2</sup> statistic. If not possible, we therefore assessed clinical heterogeneity by making qualitative comparisons in terms of the populations, interventions, outcomes/outcome measures, and methods.

**Publication Bias:** We did not perform assessment of publication bias because tests are unreliable. Excluding non-published studies - particularly those with negative results - may overestimate treatment effects.

**Notes:**  
Oxford CEBM Level of evidence 2011: EL 1 (systematic review)

**Limitations:**  
- small study groups (8-36 participants).

Johnson, M. I. et al. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. Cochrane Database Syst Rev. 8. CD007264. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: SR (no study included)</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, AMED, CINAHL,</p>	<p>Population: Adults after limb amputation resulting in any type of pain in a phantom or stump, or both.</p> <p>Intervention: TENS</p> <p>Comparison: no</p>	<p>Primary: Patient-reported pain using standard subjective validated scales (e.g. visual analogue scales (VAS) or numerical rating scales (NRS)).</p> <p>Secondary: Any other related pain measure; Patient reported non-painful phantom sensations, for others see review.</p> <p>Results: No results.</p>	<p>no studies included.</p>

<p><b>PEDRO and SPORTDiscus.</b></p> <p>Search period: 2010 to 25 March 2015.</p> <p>Inclusion Criteria: RCTs;</p> <p>Exclusion Criteria: letters, abstracts and reviews (unless they provided additional information from published RCTs that met the criteria); studies using experimental pain; case reports; clinical observations; trials that were non-randomised.</p>	<p>treatment, sham control, pharmacological intervention, non-pharmacological intervention.</p>	<p><b>Author's Conclusion:</b> There were no RCTs to judge the effectiveness of TENS for the management of phantom pain and stump pain. The published literature on TENS for phantom pain and stump pain lacks the methodological rigour and robust reporting needed to confidently assess its effectiveness. Further RCT evidence is required before an assessment can be made. Since publication of the original version of this review, we have found no new studies and our conclusions remain unchanged.</p>
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<p><b>Methodical Notes</b></p>
<p><b>Funding Sources:</b> Cochrane Review Group funding acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. <b>Disclaimer:</b> The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health.</p> <p><b>COI:</b> Mark I Johnson has no conflicts of interest to declare. Matthew R Mulvey has no conflicts of interest to declare. Anne-Marie Bagnall has no conflicts of interest to declare.</p> <p><b>Study Quality:</b> Assess risk of bias for each trial, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion.</p> <p><b>Heterogeneity:</b> tested for statistical homogeneity, by visual inspection of the forest plot and by using the Chi2 test and I2 statistic.</p> <p><b>Publication Bias:</b> -</p> <p><b>Notes:</b> Oxford CEBM Level of evidence 2011: EL 1 (systematic review)</p>

<p><b>Weinstein, E. J. et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev. 6. CD007105. 2018</b></p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: SR and META (63 studies in total - 3 regarding limb amputation)</p> <p>Databases: CENTRAL, MEDLINE, and Embase.</p> <p>Search period: Until December 2016.</p> <p>Inclusion Criteria: RCTs; single-blinded studies because regional anaesthesia causes numbness of the affected body part and, therefore, neither participant nor anaesthesia provider can be reliably blinded to the intervention. However, blinding of the outcome observer was a prerequisite for inclusion in this review.</p> <p>Exclusion Criteria: We excluded studies in participants undergoing orthopaedic procedures.</p>	<p><b>Population:</b> Adults and children after elective, non-orthopaedic surgery with a pain outcome beyond three months after surgery.</p> <p><b>Intervention:</b> Local or regional anaesthesia versus conventional analgesia.</p> <p><b>Comparison:</b> see intervention.</p>	<p><b>Primary:</b> Persistent postoperative pain (PPP) at three or more months after surgery.</p> <p><b>Secondary:</b> 1. Allodynia and hyperalgesia 2. Use of pain medication 3. Adverse effects of techniques and agents used.</p> <p><b>Results:</b> Limb amputation We did not pool two studies investigating the effect of epidural anaesthesia on chronic pain (phantom limb pain) after limb amputation at six months. PPP may be different from phantom limb pain and timing of nociception may be much more important for the latter. Pooling groups of participants receiving epidural analgesia during different pre-, intra- and postoperative intervals may be seen as arbitrary and controversial.</p> <p>For other results see text.</p> <p><b>Author's Conclusion:</b> We conclude that there is moderate-quality evidence that regional anaesthesia may reduce the risk of developing PPP after three to 18 months after thoracotomy and three to 12 months after caesarean section. There is low-quality evidence that regional anaesthesia may reduce the risk of developing PPP three to 12 months after breast cancer surgery. There is moderate evidence that intravenous infusion of local anaesthetics may reduce the risk of developing PPP three to six months after breast cancer surgery. Our conclusions are considerably weakened by the small size and number of studies, by performance bias, null bias, attrition and missing data. Larger, high-quality studies, including children, are needed. We caution that except for breast surgery, our evidence synthesis is based on only a few small studies. On</p>	<p>Karanikolas 2006; Katsuly-Liapis 1996, Pinzur 1996</p>

a cautionary note, we cannot extend our conclusions to other surgical interventions or regional anaesthesia techniques, for example we cannot conclude that paravertebral block reduces the risk of PPP aCer thoracotomy. There are seven ongoing studies and 12 studies awaiting classification that may change the conclusions of the current review once they are published and incorporated.

#### Methodical Notes

**Funding Sources:** No sources of support supplied.

**COI:** None know.

**Study Quality:** Karanikolas -low risk of bias  
Katsuly-Liapis - unclear risk of bias  
Pinzur - low to unclear risk of bias.

**We compared our results to Bayesian and classical (frequentist) models. We investigated heterogeneity. We assessed the quality of evidence with GRADE.**

**Heterogeneity:** We investigated study heterogeneity at the subgroup level using a Chi2 test and calculation of the I2 statistic.

**Publication Bias:** We considered an examination of publication bias using graphical and statistical tests (e.g. funnel plot, Egger's test).

**Notes:**  
Oxford CEBM Level of evidence 2011: EL 1 (systematic review)

**Phantom pain after amputation was only a small part of this analysis.**

Schlüsselfrage:

5.3 Kinder

Fragestellung wird durch LL-Adaptation aktualisiert. Zusätzlich wurde in 2020 eine Cochrane Update Recherche durchgeführt. Die dabei gefundenen Studien sind in dieser Sammlung zusammengefasst.

Inhalt: 7 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Black, K. J. L. 2013	1	SR (1 study included)
Erskine, A. 2015	1	SR of 3 Studies (Denmark and US (2); no studies suitable for quantitative analysis (MA)).
Feriani, G. 2016	1	SR and MA of 8 studies (prospective, randomised, controlled, and double-blind trials conducted in a single centre). India (Ahuja 1994; Gaonkar 2004; Prabhu 1999; Rajamani 2007) United States (Nicodemus 1991; Simion 2008), Turkey(Takmaz 2009) Spain (Delgado 2005)
Foster, J. P. 2017	1	SR of eight small randomised controlled trials (n = 506)
Guay, J. 2019	1	Systematic review including 11 trials (559 participants), and seven trials (249 participants) in the analysis (META)
Lambert, P. 2014	1	SR and META of 11 studies.
Stevens, B. 2016	1	SR and META of 74 studies (20 additional studies included in this update) of 22 different countries.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 7 Bewertung(en)

Black, K. J. L. et al. Nerve blocks for initial pain management of femoral fractures in children. Cochrane Database of Systematic Reviews. . . 2013			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: SR (1 study included)</p> <p>Databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (11 January 2013), the Cochrane Central Register of Controlled Trials (2012 Issue 12), MEDLINE (1946 to January Week 1 2013), EMBASE (1980 to 2013 Week 01) and Google Scholar (February Week 1 2013). We searched registries of clinical trials via clinicaltrials.gov and the World Health Organization's WHO International Clinical Trials Registry Platform (ICTRP) to identify ongoing and recently completed trials (31 January 2013).</p> <p>Search period: See Database</p> <p>Inclusion Criteria: Randomised controlled trials and quasi-randomised controlled trials (where allocation of participants to groups is by a method that is not strictly random, e.g. by date of birth, hospital record number, alternation) assessing the effects of FNB or FICB for initial pain management in children</p>	<p>Population: Children aged 18 and under with an acute femur fracture receiving pre-hospital or in-hospital emergency care. Diagnosis could be clinical with radiographic confirmation aHer enrolment.</p> <p>Intervention: We aimed to make two comparisons: 1. FNB or FICB versus placebo (sham) or no injection, wherein all participants also received another method of analgesia (e.g.</p>	<p>Primary: 1. Failure of analgesia (e.g. failure to achieve a pain score of less than 4 out of 10 on a Visual Analogue Scale (VAS) or equivalent within 30 minutes of delivery of analgesia). 2. Pain level during procedures and transfers up to eight hours post intervention. 3. Adverse outcomes related to the following methods of analgesia including - FNB -Comparison medication</p> <p>Secondary: 1. Time to pain relief in minutes 2. Duration of pain control 3. Need for additional pain control prior to immobilisation, or until eight hours after intervention. 4. Pain, discomfort and distress during application of analgesia. 5. Patient and/or parental satisfaction. 6. Use of resources.</p>	<p>Wathen 2007</p>

<p>with fractures of the femur.</p> <p>Exclusion Criteria: -</p>	<p>systemic opioids) 2. FNB or FICB versus systemic analgesia</p> <p>Comparison: see intervention.</p>	<p>Results: Wathen 2007 compared FICB with systemic analgesia (morphine) in 55 children with femoral fractures.</p> <p>Failure of analgesia: Although fewer children in the FICB group than in the morphine group had analgesia failure at 30 minutes, the difference between the two groups did not reach statistical significance (2/26 (8%) versus 8/28 (29%); risk ratio (RR) 0.33; 95% CI 0.09 to 1.20; P value 0.09).</p> <p>At 30 minutes, using the CHEOPS pain scale (range of possible values: 3 to 14; failure of analgesia values greater than or equal to 7), the mean pain score was reported as 5.87 and 7.54 in the FICB and morphine groups, respectively. The authors reported that this represented an 18% difference in favour of the nerve block (95% CI 8% to 27%), which had decreased from a mean pain score of 9.45 in both groups at baseline.</p> <p><u>Pain during procedures or transfer: n.a.</u></p> <p>Adverse outcomes: None of the differences between the two groups for individual adverse events, all typical of the type of analgesia, reached statistical significance (e.g. respiratory depression: 1/26 versus 6/28; RR 0.19, 95% CI 0.02 to 1.44).</p> <p>Author's Conclusion: This review offers weak evidence that fascia iliaca compartment block (FICB) is a useful pain management strategy in femur fractures in children. With limited participant numbers, we cannot draw conclusions regarding whether it is significantly better than systemic analgesia, but the trend appears to be in that direction, with a better safety profile. No femoral nerve block (FNB) studies met the inclusion criteria for our review.</p>
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<p><b>Methodical Notes</b></p>
<p>Funding Sources: some internal and external funding (research grant).</p> <p>COI: see publication.</p> <p>Study Quality: No blinding (high risk of blinding), randomization yes.</p> <p>Heterogeneity: n.a.</p> <p>Publication Bias: n.a.</p> <p>Notes:</p>

<p>Erskine, A. et al. As required versus fixed schedule analgesic administration for postoperative pain in children. Cochrane Database of Systematic Reviews. . . 2015</p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: SR of 3 Studies (Denmark and US (2); no studies suitable for quantitative analysis (MA)).</p> <p>Databases: 1. the Cochrane Central Register of Controlled</p>	<p>Population: Children under the age of 16 years, who had undergone any surgical procedure requiring postoperative pain relief, in any setting.</p> <p>Intervention: 1. the use of as required or 'pro re nata' (PRN) analgesia administered by any route, in any dosage, and</p>	<p>Primary: 1. Pain intensity and pain relief, assessed using validated tools such as NRS, VAS, FPS-R, Colour Analogue Scale (CAS), or any other validated NRS. We searched for participant-reported pain, but accepted observer-reported outcomes if no data were available for participant-reported pain.</p> <p>2. Any reported adverse events</p> <p>Secondary: 1. Participant global impression,</p>	<p>Rømsing 1998; Sutters 2004; Sutters 2010.</p>

<p>Trials (CENTRAL; on The Cochrane Library) Issue 6 of 12, 2014;  2. MEDLINE and MEDLINE in Process 1946 to 29 July 2014;  3. EMBASE 1947 to 29 July 2014;  4. CINAHL 1982 to July 2014.  ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP); reference lists of reviews and retrieved articles for additional studies.</p> <p>Search period: See Databases</p> <p>Inclusion Criteria:  Children undergoing tonsillectomy, aged not older than 15 years; RCTs</p> <p>Exclusion Criteria:  Studies of patient-controlled analgesia (as these are not 'PRN' in the true sense of the term ). non RCTs, no assessment of PRN versus ATC analgesic administration.</p>	<p>prescribed to treat pain postoperatively;  2. fixed analgesic administration schedules for postoperative pain management.</p> <p>Romsing (1998) 53 children, 2 groups- paracetamol (acetamoniophen, in weight appropriate doses) for the first three days, orally or rectally. Control group paracetamol PRN.  Sutters (2004) 88 children, 3 groups, paracetamol with codein (paracetamol 120 mg/5 mL with codeine 12 mg/5 mL)) for 3 days after surgery (PRN group: Dose every four Hours PRN; ATC group: every four hours ATC wo nurse coaching; ATC+coaching: every four hours with ATN with nurse coaching).  Sutters (2010) 123 children, 3 groups, as decribed in Sutters (2004), All children received elixir of paracetamol with hydrocodone in weight-appropriate doses (maximum daily paracetamol dose approximately 73 mg/kg and hydrocodone approximately 0.2 mg/kg/dose) for three days afer surgery.</p> <p>Comparison: see intervention.</p>	<p>measured using the Patients' Global Impression of Change (PGIC) scale (Hurst 2004).  2. Carer global impression; see point 1 above.  3. Medication use.  4. Requirement for rescue analgesia.  5. Length of postoperative stay.  6. Sleep duration and quality.  7. Acceptability of treatment</p> <p>Results: Pain intensity and pain relief:  Romsing: PCT, mean pain intensity scores tended to be higher in the morning than the evening, except on day one where the mean pain scores were lower in the morning (both groups).  Pain relief not reported.  Sutters (2004): NRS, There were no differences in pain intensity or pain relief scores between groups. There were no differences between pain intensity with swallowing and without swallowing.  Sutters (2010): NRS, Pain intensity scores were higher for both ATC and PRN groups in the morning than in the evening for all three days. The mean pain intensity scores were numerically but not significantly higher in the PRN group than the ATC group, both with swallowing (3.9 with PRN versus 3.0 with ATC) and without swallowing (4.2 with PRN and 3.2 with ATC). Pain relief was not reported.  See publication for other outcome results.</p> <p>Author's Conclusion: 1. For children under the age of 16 years with postoperative pain, we could not determine whether the 'around the clock' method was any different from the 'as required' method, for outpatients given oral or rectal analgesics.  2. For clinicians, at present there is insufficient evidence to recommend one approach over another. Around the clock would appear to be a logical approach based on adult studies but we have not been able to demonstrate superiority.  3. For policy-makers and funders, there can be no implications for policy-makers making recommendations on the management of postoperative pain based on this review.</p>
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<p><b>Methodical Notes</b></p> <p>Funding Sources: Neither Rømsing 1998 nor Sutters 2004 declared a funding source; Sutters 2010 was supported by a grant from the National Institute of Nursing Research, USA.</p> <p>COI: see publication</p> <p>Study Quality: All studies showed low or unclear risk of bias except regarding the size of the sample. This represents high risk of bias due to low sample size (fewer than 50 children in total or per treatment arm). Reported quality was poor of the underlying studies.</p> <p>Heterogeneity: n.a.</p> <p>Publication Bias: n.a.</p> <p>Notes:  Relevance for update unclear because only one study (Sutters 2010) was published after 2007 (literature search of the original guideline).</p>
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<p>Feriani, G. et al. Infraorbital nerve block for postoperative pain following cleft lip repair in children. Cochrane Database of Systematic Reviews. . . 2016</p>			
<p>Evidence level/Study Types</p>	<p>P - I - C</p>	<p>Outcomes/Results</p>	<p>Literature References</p>
<p>Evidence level: 1</p>	<p>Population: Children up</p>	<p>Primary: 1. Pain measured by valid</p>	<p>Ahuja 1994;</p>

<p><b>Study type:</b> SR and MA of 8 studies (prospective, randomised, controlled, and double-blind trials conducted in a single centre). India (Ahuja 1994; Gaonkar 2004; Prabhu 1999; Rajamani 2007) United States (Nicodemus 1991; Simion 2008), Turkey (Takmaz 2009) Spain (Delgado 2005)</p> <p><b>Databases:</b> Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, Issue 6, 2015), MEDLINE, EMBASE, and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS). Ongoing trials in the following platforms were checked: the metaRegister of Controlled Trials; ClinicalTrials.gov (the US National Institutes of Health Ongoing Trials Register), and the World Health Organization International Clinical Trials Registry Platform (on 17 June 2015). We also checked reference lists of the included studies to identify any additional studies. We contacted specialists in the field and authors of the included trials for unpublished data.</p> <p><b>Search period:</b> From inception to 17 June 2015.</p> <p><b>Inclusion Criteria:</b> Studies assessing children undergoing infraorbital nerve block for postoperative pain following cleft lip repair. There were no language restrictions.</p> <p><b>Exclusion Criteria:</b> Three studies were excluded because they compared different anaesthetics and because all children received infraorbital nerve block and one study because it was not randomised.</p>	<p>to 13 years of age with cleft lip repair surgery (353 children; sample sizes ranged from 20 to 82 children per study).</p> <p><b>Intervention:</b> Infraorbital nerve block Of the eight studies included three compared infraorbital nerve block with placebo, that is sham block (Ahuja 1994; Nicodemus 1991; Takmaz 2009). Three studies compared infraorbital nerve block with intravenous analgesia (Delgado 2005; Rajamani 2007; Simion 2008), and two studies compared infraorbital nerve block with anaesthetic infiltration of the incision (Gaonkar 2004; Prabhu 1999).</p> <p><b>Comparison:</b> Placebo; intravenous analgesia; infiltration of the incision</p>	<p>instruments (e.g. Neonatal Infant Pain Scale (NIPS) (Hudson-Barr 2002); the Face, Legs, Activity, Cry, Consolability (FLACC) Scale (Merkel 1997))</p> <p>2. Duration of postoperative analgesia 3. Adverse events</p> <p><b>Secondary: Secondary outcomes</b></p> <ol style="list-style-type: none"> <li>1. Need for analgesic prescription for pain</li> <li>2. Time to first analgesic requirement</li> <li>3. Heart rate, respiratory rate, and blood pressure</li> <li>4. Time to feeding after surgery</li> <li>5. Duration of hospitalisation</li> </ol> <p><b>Results:</b> 1. Infraorbital nerve block versus placebo Pain measured by valid instruments The MA (three studies that reported this outcome) showed a significant difference in favour of the intervention group in the peak of pain, measured during the postoperative period (standardised mean difference (SMD) -3.54, 95% confidence interval (CI) -6.13 to -0.95; 3 studies; 120 children; P = 0.007; I<sup>2</sup> = 94%). There was significant heterogeneity in this analysis, and the random-effects model was used. After we excluded one study (Takmaz 2009), heterogeneity disappeared (SMD -1.80, 95% CI -2.33 to -1.27; 2 studies; 80 children; P &lt; 0.00001; I<sup>2</sup> = 0%). This outcome was downgraded three levels of evidence (to very low quality) due to few studies with a limited number of children, unclear methodology of the studies, and the heterogeneity of analysis.</p> <p>2. Duration of postoperative analgesia In Nicodemus 1991, the intervention group had a significantly longer duration of analgesia than the placebo group: 19.43 ± 5.06 hours versus 11.17 ± 6.16 hours (mean difference (MD) 8.26, 95% CI 5.41 to 11.11; P &lt; 0.00001).</p> <p>3. Adverse events Ahuja 1994 reported no adverse events in the children. Takmaz 2009 reported more episodes of vomiting in the placebo than in the intervention group (40% versus 10%; P = 0.001). Nicodemus 1991 did not report this outcome.</p> <p>2. Infraorbital nerve block versus intravenous analgesia - pain The MA of Delgado 2005 and Rajamani 2007, showed a significant difference between the groups favouring the intervention group in mean peak pain measured in the first four hours after surgery (SMD -1.50, 95% CI -2.40 to -0.60; 2 studies; 107 children; P = 0.001; I<sup>2</sup> = 64%) (Analysis 2.1).</p> <p>For secondary outcomes see text.</p> <p><b>Author's Conclusion:</b> There is low-to very low-quality evidence that infraorbital nerve block with lignocaine or bupivacaine may reduce postoperative pain more than placebo and intravenous analgesia in children undergoing cleft lip repair. Further studies with larger samples are needed. Future studies should standardise the observation time and the instruments used to measure outcomes, and stratify children by age group.</p>	<p>Delgado 2005; Gaonkar 2004; Nicodemus 1991; Prabhu 1999; Rajamani 2007; Simion 2008; Takmaz 2009</p>
<p><b>Methodical Notes</b></p>			
<p><b>Funding Sources:</b> n.s.</p>			
<p><b>COI:</b> none</p>			



**Study Quality:** Oxford Quality Score to assess the methodological quality of included studies and used Cochrane's tool for assessing risk of bias tool.

The included studies were of low to moderate methodological quality. The reasons for downgrading the quality of the evidence using GRADE related to the lack of information about randomisation methods and allocation concealment in the studies, very small sample sizes, and heterogeneity of outcome reporting.

**Heterogeneity:** see publication

**Publication Bias:** see publication

**Notes:**

Foster, J. P. et al. Topical anaesthesia for needle-related pain in newborn infants. Cochrane Database of Systematic Reviews. . . 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> SR of eight small randomised controlled trials (n = 506)</p> <p><b>Databases:</b> Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase and CINAHL; previous reviews including cross-references, abstracts, and conference proceedings. We contacted expert informants. We contacted authors directly to obtain additional data. We imposed no language restrictions.</p> <p><b>Search period:</b> up to 15 May 2016</p> <p><b>Inclusion Criteria:</b> Published and unpublished randomised controlled trials (RCTs) or quasi-RCTs; we intended to include cluster and cross-over randomised trials. Trials assessing the use of topical anaesthetics such as amethocaine and EMLA in newborn term or preterm infants requiring an invasive procedure involving puncture of skin and other tissues with a needle.</p> <p><b>Exclusion Criteria:</b> Infants previously exposed to a topical anaesthetic prior to enrolment. Also excluded was topical anaesthesia during circumcision.</p>	<p><b>Population:</b> Newborn term or preterm (or both) infants up to a postnatal age of one month requiring an invasive procedure involving puncture of skin and other tissues with a needle (heel lance, venepuncture, arterial puncture, arterial cannulation, supra-pubic aspiration of urine, lumbar puncture, intramuscular injection, percutaneous venous catheter).</p> <p><b>Intervention:</b></p> <ul style="list-style-type: none"> <li>• EMLA versus placebo.</li> <li>• EMLA versus amethocaine.</li> <li>• EMLA versus other topical anaesthetic.</li> <li>• Amethocaine versus placebo.</li> <li>• Amethocaine versus other topical anaesthetic.</li> </ul> <p>Amethocaine and EMLA could be given at any dose, location or length of time as determined in each of the included studies. The topical anaesthesia could be applied using any method of delivery and any product (gel, liquid, spray, cream and any other forms).</p> <p><b>Comparison:</b> see Intervention.</p>	<p><b>Primary:</b> Pain using validated pain score (measured during the procedure, up to one hour following painful procedure or both) such as:</p> <ul style="list-style-type: none"> <li>◦ NIPS (Lawrence 1993);</li> <li>◦ PIPP (Stevens 1996);</li> <li>◦ Neonatal Facial Action Coding System (Grunau 1987);</li> <li>◦ other validated pain measures.</li> </ul> <p><b>Secondary:</b> Number of infants with methaemoglobin levels 5%, Number of needle prick attempts prior to successful needle related procedure, Total cry duration...</p> <p><b>Results:</b> Pain: We were unable to meta-analyse the outcome of pain due to differing outcome measures and methods of reporting.</p> <p>For EMLA, two individual studies reported a statistically significant reduction in pain compared to placebo during lumbar puncture and venepuncture. Three studies found no statistical difference between the groups during heel lancing. For amethocaine, three studies reported a statistically significant reduction in pain compared to placebo during venepuncture and one study reported a statistically significant reduction in pain compared to placebo during cannulation. One study reported no statistical difference between the two groups during intramuscular injection. One study reported no statistical difference between EMLA and the placebo group for successful venepuncture at first attempt. One study similarly reported no statistically significant difference between Amethocaine and the placebo group for successful cannulation at first attempt.</p> <p>Bonetto 2008 used the 0 to 18 PIPP score for infants over 36 weeks' gestation and reported no statistical difference between the EMLA and placebo groups from insertion of heel lance and up to three minutes, using the PIPP score (MD 0.27, 95% CI -1.45 to 1.99; n = 38). The PIPP score used was a seven-indicator measure; a score of less than 8 indicated absence or minimal pain and a score greater than 8 indicated moderate pain from a maximum score of 18 (Analysis 1.1). The quality of evidence was low due to results from only one small study.</p> <p>Bonetto 2008 measured pain during heel lancing using the NIPS and reported no significant difference between the EMLA and placebo groups (MD 0.27, 95% CI -0.75 to 1.29; n = 38). A NIPS score of 0 indicated no pain, and a maximum score of 7 indicated moderate-to-severe pain (Analysis 1.2). The quality of evidence was low due to results from only one small study.</p> <p>Shah 2008 used the Facial Grimacing Score to measure pain during intramuscular injection. The score ranged from 0% to 100%. There was no statistically significant difference between the two groups (MD -5.00, 95% CI -17.34 to 7.34; n = 110) (Analysis 2.1). The quality of evidence was low due to</p>	<p>Bonetto 2008 (n = 38); Jain 2000a (n = 39); Kaur 2003 (n = 60); Larsson 1995 (n = 110); Larsson 1998 (n = 111); Long 2003 (n = 32); Shah 2008 (n = 110); Stevens 1999 (n = 106).</p>

results from only one small study.

**Author's Conclusion:** Overall, all the trials were small, and the effects of uncertain clinical significance. The evidence regarding the effectiveness or safety of the interventions studied is inadequate to support clinical recommendations. There has been no evaluation regarding any long-term effects of topical anaesthetics in newborn infants. High quality studies evaluating the efficacy and safety of topical anaesthetics such as amethocaine and EMLA for needle-related pain in newborn term or preterm infants are required. These studies should aim to determine efficacy of these topical anaesthetics and on homogenous groups of infants for gestational age. While there was no methaemoglobinaemia in the studies that reported methaemoglobin, the efficacy and safety of EMLA, especially in very preterm infants, and for repeated application, need to be further evaluated in future studies.

**Methodical Notes**

**Funding Sources:** None

**COI:** None

**Study Quality:** We used the standardised review methods of the Cochrane Neonatal Review Group (CNRG) to assess the methodological quality of included studies ([neonatal.cochrane.org/en/index.html](http://neonatal.cochrane.org/en/index.html)) and assessed study quality and risk of bias using the following criteria documented in the Cochrane Handbook for Systematic Reviews of Interventions. Risk of bias was low in all studies.

**Heterogeneity:** Planned to assess, but not applicable.

**Publication Bias:** Assessed

**Notes:**

The impact of the review is unclear, because only the studies of Bonetto (n= 38, 2008, Argentina, EMLA for pain in newborn during heel lancing) and Shah (n= 110, 2008, topical amethocaine gel 4% in neonates undergoing intramuscular injection, Canada) were published after the systematic literature search was conducted for the Guideline Akutschmerz in 2006/2007. All other studies were published before 2003.

**Guay, J. et al. Postoperative epidural analgesia versus systemic analgesia for thoraco?lumbar spine surgery in children. Cochrane Database of Systematic Reviews. . . 2019**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p><b>Evidence level:</b> 1</p> <p><b>Study type:</b> Systematic review including 11 trials (559 participants), and seven trials (249 participants) in the analysis (META)</p> <p><b>Databases:</b> Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and Cumulative Index to Nursing and Allied Health Literature, together with the references lists of related reviews and retained trials, and two trials registers.</p> <p><b>Search period:</b> From implementation until 14 November 2018.</p> <p><b>Inclusion Criteria:</b> Randomized controlled trials (RCTs) evaluating epidural analgesia for postoperative pain in children (aged 0 to 18 years), and comparing epidural analgesia with any form of systemic analgesia by any route. No restrictions on the basis of language of publication or publication status. Participants were undergoing thoracic, lumbar, or thoraco-lumbar spine surgery. We included studies using any</p>	<p><b>Population:</b> Children undergoing any type of thoraco-lumbar spine surgery; three trials included in the analysis contained some participants older than 18 years (Four trials included participants older than 18 years: Blumenthal 2005 (10 to 30 years; mean age 17 years); Ezhevskaya 2012a (12 to 25 years); Klatt 2013 (10 to 21 years); and O'Hara 2004 (13 to 21 years)).</p> <p><b>Intervention:</b> epidural analgesia (n= 140 participants), for example: investors administered epidural analgesia as a single shot block or as a continuous infusion for any duration and containing a local anaesthetic alone (extended duration or not) or in combination with an opioid (extended duration or not) or an opioid alone. We included studies in</p>	<p><b>Primary:</b> 1. Pain (at rest and on movement up to 72 hours after surgery). We included pain measured on any ascending or descending scale as provided by study authors. 2. Vomiting up to 48 hours after surgery (number of participants with event). We extracted data on this outcome as the number of participants who experienced vomiting episodes. 3. Return of gastrointestinal function measured as time to first: i) flatus (hours); ii) bowel movement (hours); iii) liquid ingestion (hours); iv) solid food ingestion (hours).</p> <p><b>Secondary:</b> 1. Time to first mobilization (days). 2. Hospital length of stay (days). 3. Satisfaction with postoperative analgesia regimen 4. Complications</p> <p><b>Results:</b> Main results_Pain: Compared with systemic analgesia, epidural analgesia reduced pain at rest at all time points. At six to eight hours, the mean pain score on a 0 to 10 scale with systemic analgesia was 3.1 (standard deviation 0.7) and with epidural analgesia was -1.32 points (95% confidence interval</p>	<p>Blumenthal 2005; Blumenthal 2006; Cakar Turhan 2011; Cassady 2000; Ezhevskaya 2012a; Ezhevskaya 2015; Gauger 2009; Klatt 2013; Malviya 1999; O'Hara 2004; Ozturk Mamik 2011</p>

surgical approach: minimally invasive or not, posterior or anterior or both, and located at the thoracic or lumbar or thoraco-lumbar level.

Exclusion Criteria: Observational studies, quasi-randomized trials, cross-over trials, and cluster-randomized trials were excluded. As well we excluded studies in which investigators added substances directly in the epidural space without the use of an epidural needle/catheter, such as steroids or other substances (gelfoam soaked or microfibrillar collagen or other). We excluded studies in which researchers administered the local anaesthetic or the opioid intrathecally. We excluded trials comparing nerve blocks versus systemic analgesia.

which trialists added an adjuvant to the solution or not.

Comparison: systemic analgesia (n= 109).

(CI) -1.83 to -0.82; 4 studies, 116 participants; moderate-quality evidence). At 72 hours, the mean pain score with epidural analgesia was equivalent to a -0.8 point reduction on a 0 to 10 scale (standardized mean difference (SMD) -0.65, 95% CI -1.19 to - 0.10; 5 studies, 157 participants; moderate-quality evidence). Gastrointestinal function: There was no difference for nausea and vomiting between groups (risk ratio (RR) 0.87, 95% CI 0.58 to 1.30; 6 studies, 215 participants; low-quality evidence).

Secondary outcome: (unclear\_uncertain difference in results)  
time to ambulate (MD 0.08 days, 95% CI -0.24 to 0.39; 1 study, 60 participants; very low-quality evidence)  
hospital length of stay (MD -0.29 days, 95% CI -0.69 to 0.10; 2 studies, 89 participants; very low-quality evidence).  
participants satisfied when treated with epidural analgesia (MD 1.62 on a scale from 0 to 10, 95% CI 1.26 to 1.97; 60 participants- 2 studies; very low-quality evidence).  
parent satisfaction for epidural analgesia with an opioid alone (MD 0.60, 95% CI -0.81 to 2.01; 1 trial, 27 participants; very low-quality evidence).  
 It was uncertain whether there was a difference in the risk of complications.

Author's Conclusion: There is moderate- and low-quality evidence that there may be a small additional reduction in pain up to 72 hours after surgery with epidural analgesia compared with systemic analgesia. Two very small studies showed epidural analgesia with local anaesthetic alone may accelerate the return of gastrointestinal function. The safety of this technique in children undergoing thoraco-lumbar surgery is uncertain due to the very low quality of the evidence.

**Methodical Notes**

Funding Sources: Was assessed - see publication for details.

COI: None.

Study Quality: The quality of included studies was assessed using the Cochrane 'Risk of bias' tool. We judged the quality of the body of evidence according to the GRADE system and presented this assessment in Summary of findings for the main comparison for all outcomes, using the GRADEpro software. When possible, the data were entered into an intention-to-treat (ITT) analysis.

Risk of bias was low (or unclear) for all studies - except performance and detection bias, which was assessed high in about 25% of the studies (for details see publication).

Heterogeneity: We considered clinical heterogeneity before pooling results, and examined statistical heterogeneity before carrying out any metaanalysis. Heterogeneity was low.

Publication Bias: We assessed publication bias using a funnel plot and some studies identified with publication bias - see publication for details.

Notes:

Lambert, P. et al. Clonidine premedication for postoperative analgesia in children. Cochrane Database of Systematic Reviews. . . 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1	Population: children	Primary: 1. The number of children requiring an additional analgesia intervention in the post-anaesthesia care unit	see publication

<p>Study type: SR and META of 11 studies.</p> <p>Databases: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Issue 12, 2012), Ovid MEDLINE (1966 to 21 December 2012) and Ovid EMBASE (1982 to 21 December 2012). We did not apply language or publication restrictions.</p> <p>Ongoing clinical trials via 1. <a href="http://www.controlled-trials.com">http://www.controlled-trials.com</a>; 2. <a href="http://www.update-software.com">http://www.update-software.com</a>; 3. <a href="http://clinicalstudyresults.org">http://clinicalstudyresults.org</a>; 4. <a href="http://centrewatch.com">http://centrewatch.com</a>.</p> <p>Search period: see Database.</p> <p>Inclusion Criteria: All randomized and quasi-randomized, published and unpublished, controlled clinical studies. Studies with clonidine as premedication for any anaesthetic, regardless of the type of surgery; any route of administration unless it was used systemically.</p> <p>Exclusion Criteria: We excluded:</p> <ul style="list-style-type: none"> <li>- observational studies;</li> <li>- dose-finding studies except where one arm of the trial equated to a placebo or comparison treatment;</li> <li>- studies with significant confounding factors;</li> <li>- studies where more than one treatment had been changed, for example clonidine and ketamine versus midazolam alone;</li> <li>- where clonidine had been given after induction of anaesthesia.</li> </ul>	<p>(n=742) undergoing surgery and receiving analgesia and clonidine as premedication.</p> <p>Intervention: Clonidine may be given orally, per rectum or parenterally prior to surgery. It may be given as the sole premedication or in conjunction with other drugs.</p> <p>Comparison: placebo or other drug treatment (midazolam, fentanyl or higher dose of clonidine) or no intervention at all.</p>	<p>(PACU);</p> <ol style="list-style-type: none"> <li>2. The number of children requiring an additional analgesia intervention at any time postoperatively, defined as for interventions in PACU, above.</li> <li>3. The number of children with sedation requiring intervention.</li> </ol> <p>Secondary:</p> <ol style="list-style-type: none"> <li>1. The number of children requiring opioid analgesia postoperatively.</li> <li>2. The number of children pain-free in PACU.</li> <li>3. Postoperative pain as measured by the investigators. This can include a pain score, e.g. by visual analogue scale (VAS) or verbal numerical rating score (VNRS).</li> </ol> <p>4-13 (see publication)</p> <p>Results: <u>Analgesia intervention in the post anaesthesia care unit (PACU) and additional analgesia at any time postoperatively.</u></p> <p>When clonidine was compared to placebo, pooling studies of low or unclear risk of bias, the need for additional analgesia was reduced when clonidine premedication was given orally at 4 µg/kg (risk ratio (RR) 0.24, 95% confidence interval (CI) 0.11 to 0.51). Only one small trial (15 patients per arm) compared clonidine to midazolam for the same outcome; this also found a reduction in the need for additional postoperative analgesia (RR 0.25, 95% CI 0.09 to 0.71) when clonidine premedication was given orally at 2 or 4 µg/kg compared to oral midazolam at 0.5 mg/kg. A trial comparing oral clonidine at 4 µg/kg with intravenous fentanyl at 3 µg/kg found no statistically significant difference in the need for rescue analgesia (RR 0.89, 95% CI 0.56 to 1.42). When clonidine 4 µg/kg was compared to clonidine 2 µg/kg, there was a statistically significant difference in the number of patients requiring additional analgesia, in favour of the higher dose, as reported by a single, higher-quality trial (RR 0.38, 95% CI 0.23 to 0.65).</p> <p>Post operative pain score was assessed only in two studies, both published before 2007 (Mikawa 1996; Nishina 2000), so both might be included in the literature analysis of the guideline 2007.</p> <p>Both studies used OPS and pooled there was a significant difference in the pain scores, in favour of clonidine: the standardized mean difference (SMD) was -1.11 (95% CI -1.46 to -0.75).</p> <p>Author's Conclusion: There were only 11 relevant trials studying 742 children having surgery where premedication with clonidine was compared to placebo or other drug treatment. Despite heterogeneity between trials, clonidine premedication in an adequate dosage (4 µg/kg) was likely to have a beneficial effect on postoperative pain in children. Side effects were minimal, but some of the studies used atropine prophylactically with the intention of preventing bradycardia and hypotension. Further research is required to determine under what conditions clonidine premedication is most effective in providing postoperative pain relief in children.</p>
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<p><b>Methodical Notes</b></p>
<p>Funding Sources: Anaesthesia Research at the Women's and Children's Hospital, Australia.</p> <p>COI: See publication</p> <p>Study Quality: All studies were reported as randomized, controlled and blinded except one (Schmidt 2007), which was described as open-label. Risks of bias in the studies were mainly low or unclear, but two studies had aspects of their methodology that had a high risk of bias. Quality was low or had an unclear risk of bias.</p> <p>Heterogeneity: The included studies displayed some methodological heterogeneity.</p> <p>Publication Bias: see publication.</p> <p>Notes: Relevance unclear, because the review is from 2014 and the included studies showed a high heterogeneity in study design and small sample sizes.</p>

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: SR and META of 74 studies (20 additional studies included in this update) of 22 different countries.</p> <p>Databases: MEDLINE (PubMed;1950 to February 2016), EMBASE (1980 to February 2016), CINAHL (1982 to February 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2016); ISRCTN database (www.isrctn.com), the National Institute of Health Clinical Trials database (clinicaltrials.gov), and the International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) in February 2016.</p> <p>Search period: see database</p> <p>Inclusion Criteria: Randomised controlled trials (RCTs) that evaluated the effect of sucrose analgesia in newborn infants undergoing painful procedures and (since 2012 update) any minor painful procedure (i.e. other than heel lance and venipuncture), as well as after repeated doses of sucrose; only published studies (no abstracts); no language restrictions;</p> <p>Exclusion Criteria: quasi-randomised trials, abstracts (as we have identified discrepancies in numbers of infants enrolled between abstracts and final publications).</p>	<p>Population: Term, preterm, or both term and preterm neonates, with maximum postnatal age of 28 days after reaching 40 weeks' postmenstrual age (PMA); n=7049 infants.</p> <p>Intervention: included:                      - administration of sucrose via oral syringe, dropper or in addition to a pacifier for treatment of procedural pain                      - sucrose as an intervention for any acute painful procedure including heel lance, venipuncture, subcutaneous injection, intramuscular injection, arterial puncture, circumcision, bladder catheterization, insertion of orogastric or nasogastric tube, and eye examination for retinopathy of prematurity (ROP).                      - echocardiography</p> <p>Comparison:                      - breastfeeding, breast milk or milk formula, water (sterile, tap, distilled, spring), local anaesthetics, pacifier, positioning/containing, facilitated tucking, warmth no treatment, and various concentrations of glucose                      - laser acupuncture</p>	<p>Primary: - Composite pain score                      - Multidimensional behavioural pain score f.e. PIPP, PIPP-R, DAN, NIPS, NFCS, NAPI (see publication for detail)                      - Long-term neurodevelopmental outcomes</p> <p>Secondary: - Individual behavioural pain indicators (cry duration, proportion of crying, ...)                      - Individual physiological pain indicators (heart rate, respiratory rate, oxygen saturation, ...)</p> <p>Results: Heel lance                      Heel lance was the most common painful procedure and was included in 38 studies:  <u>sucrose (20% to 30%) vs. water</u> significantly reduced NIPS scores during heel lance (indicating less pain with sucrose; moderate quality evidence).  <u>PIPP scores at 30 s or 60s</u> after heel lance: no significant differences  <u>DAN scores 30 s</u> after heel lance: no sign. diff.</p> <p>Sucrose (24%) was a more effective analgesic than breastfeeding (low quality evidence).                      For sucrose (24%) + NNS compared with water + NNS, or pacifier dipped in sucrose compared with pacifier dipped in water there was high quality evidence that PIPP scores at 30 s and 60 s were significantly reduced (indicating less pain) and that the NFCS score was non-significantly reduced.                      PIPP 30 s after heel lance WMD -1.70 (95% CI -2.13 to -1.26; I<sup>2</sup> = 0% (no heterogeneity); 3 studies, n = 278);                      PIPP 60 s after heel lance WMD -2.14 (95% CI -3.34 to -0.94; I<sup>2</sup> = 0% (no heterogeneity); 2 studies, n = 164).</p> <p>No significant difference was found between sucrose (24%) + NNS + NIDCAP compared with breast milk (by breastfeeding or by syringe) (low quality evidence). for more see publication.</p> <p>Venipuncture:                      There was high-quality evidence for the use of 2 mL 24% sucrose prior to venipuncture: PIPP during venipuncture WMD -2.79 (95% CI -3.76 to -1.83; I<sup>2</sup> = 0% (no heterogeneity); 2 groups in 1 study, n = 213); and                      intramuscular injections: PIPP during intramuscular injection WMD -1.05 (95% CI -1.98 to -0.12; I<sup>2</sup> = 0% (2 groups in 1 study, n = 232).</p> <p>Author's Conclusion: To date, the best studied use of sucrose is for heel lance, venipuncture and intramuscular injections and for these interventions sucrose appears to offer pain relief.                      Sucrose does not seem to relieve the pain associated with circumcision adequately and there is no strong indication that further studies are indicated. For pain/stress associated with arterial puncture, subcutaneous injection, bladder catheterization, orogastric or nasogastric tube insertion, ROP examination and echocardiography examination further research is warranted. For these procedures, we would recommend that if trials are done, a rescue dose should be available for infants in obvious distress, where the sucrose alone does not</p>	<p>see publication</p>

seem to be effective in preventing moderate to severe pain.

**Methodical Notes**

**Funding Sources:** see publication

**COI:** see publication

**Study Quality:** The quality of the evidence varied from low to high - for details see publication. Most studies had a small sample size: the sample sizes ranged from 15 to 671 infants, and 48 studies reported on fewer than 100 infants.

**Heterogeneity:** For most outcomes we included the results of a single study only, and so tests for heterogeneity were not applicable.

**Publication Bias:** Was assessed, but not applicable, as only three or fewer studies were included in each analysis.

**Notes:**

Type of interventions are very diverse, often only one or two studies with the same design.

Schlüsselfrage:

5.4.2 Risikofaktoren für postoperative Schmerzen

Haben operierte Patienten (P) mit bestimmten Personen-, Anästhesie- und Operationsmerkmalen (I) im Vergleich zu Patienten ohne diese Merkmale (C) ein erhöhtes Risiko für starke postoperative Akutschmerzen oder für die Entwicklung chronischer postoperativer Schmerzen (O)?

Inhalt: 10 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Baert, I. A. 2016	1	Systematic review (16 studies)
Dorow, M. 2017	1	Systematic review (21 studies included). Risk factors for postoperative pain in lumbar disc surgery patients.
Duan, G. 2018	1	Systematic review and meta-analysis (37 studies) A SR and MA was performed to investigate the risks associated with anterior knee pain (AKP) following primary total knee arthroplasty (TKA).
Hernandez, C. 2015	1	Systematic review (37 studies). To analyze pre-surgical predictive factors of post-surgical pain in patients undergoing hip or knee arthroplasty.
Hinrichs-Rocker, A. 2009	2	Systematic review (50 studies)
Khatib, Y. 2015	1	Systematic review: (19 studies) Whether (1) psychological factors, as measured by preoperative self-reported questionnaires, predicted poor outcome after TKA, and (2) whether certain psychological factors examined predicted poor outcome better than others
Lesin, M. 2015	1	Systematic review (12 studies)
Tolver, M. A. 2012	2	Systematic review (71 studies)
Wang, L. 2016	2	Systematic review and meta-analysis (30 studies) We conducted a systematic review and meta-analysis of observational studies to explore factors associated with persistent pain among women who have undergone surgery for breast cancer.
Wyld, V. 2017	1	Systematic review (14 included studies) Patientrelated risk factors for chronic pain after total knee replacement.

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 10 Bewertung(en)

Baert, I. A. et al. Does pre-surgical central modulation of pain influence outcome after total knee replacement? A systematic review. <i>Osteoarthritis Cartilage</i> . 24. 213-23. 2016			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review (16 studies)</p> <p>Databases: PubMed and Web of Science.</p> <p>Search period: Inception - up to December 2014.</p> <p>Inclusion Criteria: To be included in the systematic review, articles had to report results of studies that evaluated the influence of pre-surgical</p>	<p>Population: patients with knee osteoarthritis (OA) awaiting total knee replacement (TKR).</p> <p>Intervention: Exposure: presurgical biopsychosocial indices of</p>	<p>Primary: post-surgical outcomes: pain, function, QoL</p> <p>Secondary: -</p> <p>Results: Study characteristics: 16 studies prospective cohort studies; number of patients ranged from 4339 to 24.129 and the follow-up period after surgery ranged from 6 weeks to 5 years. 14 studies evaluated influences of central pain modulation on post-surgical outcome measure pain, 10 on function and 1 on QoL. Various questionnaires were used to obtain post-surgical outcome.</p>	<p>16 studies included:</p> <p>Brander 2003, Faller 2003, Brander 2007, Lundblad 2008, Forsythe 2008, Sullivan 2009, Edwards 2009, Riddle 2010, Sullivan 2011, Lopez-Olivo 2011, Masselin-Dubois 2013,</p>

<p>biopsychosocial measures of central pain modulation (I) on postsurgical outcome measures, such as pain, functional ability and QoL (O) in patients diagnosed with end-stage knee OA awaiting TKR surgery (P). All study designs except reviews and meta analyses were allowed (S). Study designs had a minimum follow-up period of 6 weeks. Full text record in English, French, Dutch or German.</p> <p>Exclusion Criteria: If eligibility criteria were not fulfilled, the article was excluded.</p>	<p>central pain modulation (direct and indirect pain biomarkers)</p> <p>Comparison: Non-exposure.</p>	<p>The Western Ontario and McMaster Universities Arthritis Index questionnaire (WOMAC) was the most commonly used questionnaire to measure pain, function and QoL.</p> <p>Results: only summary results available here due to length: strong evidence is available that the presence of catastrophic thinking and poor coping strategies predict more pain after TKR and that there is no association between fear of movement and post-surgical pain or knee function (conclusion strength 1). Limited evidence was found for an influence of depression on post-surgical QoL and for coping strategies on postsurgical knee function (conclusion strength 3). There is conflicting evidence for the role of depressive symptoms and anxiety in predicting pain and knee function post-surgery, as well as for the role of pain catastrophizing in predicting knee function (conclusion strength 3).</p> <p>Author's Conclusion: "In conclusion, as the economic impact of severe, unexplained pain after TKR is profound, surgeons should be attentive for patients with signs of altered central pain modulation before surgery as they might be at risk for unfavorable outcome after TKR. A broader therapeutic approach aiming to desensitize the central nervous system can be adapted in these patients. Further research is needed to identify the role of central pain modulation in predicting outcome after TKR and to address questions concerning the effectiveness of interventions that target different aspects such as the central nervous system, in contrast to therapeutic modalities only directed to structural knee joint pathology."</p>	<p>Wylde 2013, Yakobov 2014, Hanusch 2014, Utrillas-Compained 2014, Attal 2014</p>
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**Methodical Notes**

**Funding Sources:** This study was not financially supported.

**COI:** The authors declare that they have no conflicts of interest.

**Study Quality:** Risk of bias of the different studies was assessed using a checklist for cohort studies, provided by the Dutch Institute for Healthcare Improvement (CBO). Each question was answered using 'yes', 'no' or 'unclear'. The sum of all positively scored items, provided a total score for each study, transformed into a percentage. Studies with methodological quality lower than 50% were excluded. The overall level of evidence for each pre-surgical predictor was also rated with the Evidence-Based Guideline Development (EBRO) approach, an initiative of the Dutch Cochrane Center and the Dutch Institute for Healthcare Improvement (www. cbo.nl). In accordance with this methodology, selected papers were classified according to their methodological quality and strength of evidence: A1: systematic review including at least two independent A2-level studies; A2: prospective cohort study of substantial size and sufficiently long follow-up period, adequate control of confounders and minimal chance of selective drop-out during follow-up; B: prospective cohort study, but not having all characteristics of an A2 stud, or a retrospective cohort study or casecontrolled trial; C: non-comparative study; and D: expert opinion. Methodological quality was assessed independently by two researchers (SN and IB), who were blinded from each other's assessment.

**Heterogeneity:** Not applicable, meta-analysis was not performed.

**Publication Bias:** Publication bias not investigated.

**Notes:**  
Oxford level of evidence: 1 Systematic review and meta-analysis.

**Dorow, M. et al. Risk Factors for Postoperative Pain Intensity in Patients Undergoing Lumbar Disc Surgery: A Systematic Review. PLoS One. 12. e0170303. 2017**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review (21 studies included).</p> <p>Risk factors for postoperative pain in lumbar disc surgery</p>	<p>Population: Patients undergoing lumbar disc surgery.</p>	<p>Primary: Postsurgical pain: short-term outcomes (up to 3 months after surgery), medium-term outcomes (more than 3 but less than 12 months after surgery) and long-term outcomes (at least 12 months after surgery).</p>	<p>21 articles: Akagi 2010, Arpino 2004, Asch 2000, Basler&amp;Zimmer 1997,</p>



patients.  
Databases: Web of Science, Pubmed, PsycInfo and Pubpsych.

Search period: Inception - April 2015

Inclusion Criteria: English and German-language studies were included that (1) presented longitudinal observational studies with a pre- and postoperative assessment point, (2) involved a patient population undergoing surgery for the primary diagnosis of lumbar herniated disc, (3) assessed the patients' pain intensity according to a visual analogue scale, (4) assessed associations of pain intensity, and (5) presented the methodological characteristics used.

Exclusion Criteria: Studies in which patients underwent surgery primarily due to spinal diseases other than lumbar disc herniation were excluded. In order to reduce heterogeneity of surgical procedures and to include a high proportion of patients treated with the standard surgical procedure, open discectomy with or without a microscope, studies involving patients treated with minimally invasive methods and lumbar fusion were excluded. Intervention studies were excluded as we wanted to examine the natural course of postsurgical pain. Studies involving a mixed population of patients undergoing surgery and patients treated with conservative methods were excluded, unless results were presented separately for type of treatment. Finally, we excluded studies with sample sizes smaller than 30.

Intervention: Exposure to risk factors.

Comparison: Non-exposure to risk factors.

Secondary: -

Results: From 371 abstracts, 85 full-text articles were reviewed, of which 21 studies were included. Visual analogue scales indicated that surgery helped the majority of patients experience significantly less pain. Recovery from disc surgery mainly occurred within the short-term period and later changes of pain intensity were minor. Postsurgical back and leg pain was predominantly associated with depression and disability. Preliminary positive evidence was found for somatization and mental well-being.

Author's Conclusion: The objectives of this review were (1) to examine how pain intensity changes over time in disc surgery patients and (2) to identify factors associated with pain intensity. In conclusion, average pain scores were moderate to severe before surgery and only mild to moderate after surgery. In addition, the short-term postoperative outcome seems to be a reliable predictor of the longterm outcome, because later changes of pain intensity were minor. This review revealed several significant associations with pain intensity in disc surgery patients. These are of high relevance when it comes to selecting patients with uncertain indications for surgery due to herniated disc and identifying patients at risk for developing chronic pain. The most salient factor for ongoing postsurgical pain was depression. Rather than performing a unimodal surgical treatment, a multimodal treatment setting including a cooperating interdisciplinary team seems necessary to achieve substantial and long-lasting pain relief in patients who undergo surgery for disc herniation. Therefore, screening instruments should routinely be applied to identify those disc surgery patients who are in need of concomitant psychological treatment. Individualized support may positively influence the compliance during rehabilitation, which in turn may lead to a faster recovery and improved long-term outcomes. The effectiveness of additional psychological interventions needs to be studied in disc surgery patients in future research.

Chaichana 2011, D'Angelo 2010, Den Boer 2006, Folman 2008, Graver 1999, Häkkinen 2003, Hegarty & Shorten 2012, Johansson 2010, Junge 2010, Lebow 2012, Moranjkic 2010, Ng&Sell 2004, Ohtori 2010, Silverpats 2010, Sörлие 2012, Strömqvist 2008,

#### Methodical Notes

Funding Sources: We acknowledge support from the German Research Foundation (DFG) and Universität Leipzig within the program of Open Access Publishing.

COI: The authors have declared that no competing interests exist.

Study Quality: To assess the quality of the included studies, the Downs & Black (DB) checklist was applied by two independent reviewers. This checklist consists of 27 items on the domains reporting, external validity, bias, confounding and power. Unlike the original version, we used binary scoring for the power item, with 1 indicating adequate power calculations and 0 indicating that power was not adequately addressed. DB scores are divided into four quality categories: excellent (26-28), good (20-25), fair (15-19), and poor ( $\leq 14$ ) [31]. Only a randomized control study can reach the maximum score, but the checklist is also applicable for non-randomized cohort studies.

Heterogeneity: Not applicable. Systematic review no meta-analysis.

Publication Bias: Not investigated.

Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis.

Duan, G. et al. Different Factors Conduct Anterior Knee Pain Following Primary Total Knee Arthroplasty: A Systematic Review and Meta-Analysis. *J Arthroplasty*. 33. 1962-1971 e3. 2018

Evidence level/Study

P - I - C

Outcomes/Results

Literature References

Types			
<p>Evidence level: 1</p> <p>Study type: Systematic review and meta-analysis (37 studies)</p> <p>A SR and MA was performed to investigate the risks associated with anterior knee pain (AKP) following primary total knee arthroplasty (TKA).</p> <p>Databases: MEDLINE, Embase, and Cochrane Central</p> <p>Search period: Inception - July 2017)</p> <p>Inclusion Criteria: (1) published English, full-text, peer-reviewed articles; (2) a study was performed to examine risk factors for AKP, and cases and controls were defined based on the presence or absence of AKP following primary TKA; and (3) sufficient data were published for estimating an odds ratio (OR) or weighted mean difference (WMD) with 95% confidence intervals (CIs).</p> <p>Exclusion Criteria: Studies were excluded if the incidence of AKP was unable to be</p>	<p>Population: Patients undergoing primary total knee arthroplasty (TKA).</p> <p>Intervention: Exposure to risk factors.</p> <p>Comparison: Non-exposure to risk factors.</p>	<p>Primary: Anterior knee pain (AKP)</p> <p>Secondary: -</p> <p>Results: A subgroup analysis revealed that compared with those without the following medical conditions, patients who had an infrapatellar fat pad excision and more than 12 months of follow-up (odds ratio [OR] 12.58, 95% confidence interval [CI] 3.245-48.781) were more likely to have AKP after TKA. Circumpatellar electrocautery (&gt;12 months: OR 0.50, 95% CI 0.326-0.760; &lt;12 months: OR 0.59, 95% CI 0.408-0.867) and patellar resurfacing (OR 0.25, 95% CI 0.131-0.485) may decrease the risk of AKP. Other factors, including the prosthesis bearing type (mobile bearing or fixed bearing) and the approach (midvastus compared with the medial parapatellar approach), were not significant risk factors for AKP. Conclusion: The use of strategies such as patellar denervation and patellar resurfacing in primary TKA is recommended because they are safe and result in good clinical outcomes in preventing AKP. Caution should be taken when using an infrapatellar fat pad excision, because there is an increased risk of AKP at long-term follow-up (&gt;12 months). Future studies should investigate these different strategies to confirm the underlying mechanisms and help prevent the occurrence of AKP after TKA. The timing of AKP onset remains unclear and requires further research</p> <p>Author's Conclusion: This meta-analysis of currently available evidence indicates that patellar denervation and patellar resurfacing can significantly relieve AKP postoperatively after TKA. The use of these strategies in primary TKA is recommended because they are safe and result in good clinical outcomes in controlling AKP. Infrapatellar fat pad excision is a significant risk factor for AKP at more than 12 months of follow-up but not at less than 12 months of follow-up. Thus, caution should be taken when performing an infrapatellar fat pad excision. Larger, multicenter, blinded, randomized, controlled trials would provide more conclusive results. As the exact mechanisms behind the development of AKP and the timing of its onset are still unclear, future research should investigate the mechanisms of AKP and its clinical importance.</p>	<p>37 studies included: Maradit-Kermers 2017, Bae 2016, Atzori 105, Zha 2014, van Jonbergen 2014, Pinsornsak 2014, Metsan 2014, Berugem 2014, Johnson 2012, Bourke 2012, Baliga 2012, van Jonbergen 2011, Tabutin 2005, Macule 2005, Larson 20001, Kulkarni 2000, Fern 1992, Clemetns 2010, Feczko 2017, Ranawar 2016, Breugem 2008, Feczko 2016, Liu 2012, Sun 2012, Lee 2013, Li 2012, Hwang 2012, Beaupre 2012, Patel 2011, Garneti 2008, Lybäck 2004, Lindstrand 2001, Alomran 2015, Tanaka 2003, Saoud 2004, Pulavarti 2014, Pongcharoen 2013.</p>

obtained directly or indirectly. When there were discrepancies on the studies included, the authors were able to reach a consensus.

**Methodical Notes**

Funding Sources: n.a.

COI: No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work.

Study Quality: The methodological quality of the studies was independently evaluated by 2 authors, without masking the trial names. The randomized controlled trials (RCT) were evaluated using the modified Jadad scale. The 19 RCTs were relatively well designed, and the quality assessment score was high in most of them, with a range from 4 to 8 points.

Heterogeneity: Heterogeneity between studies was tested qualitatively using Q-test statistics with significance set at  $P < .10$  and a second measure was tested using  $I^2$  statistics, with an  $I^2$  more than 50% indicating moderate-to-high heterogeneity. If between-study heterogeneity was absent ( $P > .10$  or  $I^2 < 50\%$ ), the fixed-effects model was used to calculate pooled ORs or WMDs; otherwise, a random-effects model was selected.

"Moreover, 4 studies were identified that were the source of statistical heterogeneity for patellar resurfacing. This may have been due to the specific prosthesis used and the incidence of revision due to AKP. When these 4 studies were removed, there was no evidence of heterogeneity in the 4 remaining studies ( $P = .259$ ,  $I^2 \frac{1}{4} 19.3\%$ ), indicating that patellar resurfacing may decrease the risk of AKP (OR 0.12, 95% CI 0.088- 0.171) ."

Publication Bias: We assessed the possibility of publication bias by constructing a funnel plot based on each trial's effect size. We assessed funnel plot asymmetry using Begg and Egger tests, and defined significant publication bias as a P-value  $< .1$ . the trim-and-fill computation was used to estimate effect of publication bias on interpretation results.> "There was publication bias evident on the Egger test ( $P = .075$ ; Supplementary Table 1). However, further analysis with the trim-and-fill test indicated that this publication bias did not impact the estimates (no trimming done and the data unchanged)."

Notes:

Oxford level of evidence: 1 Systematic review and meta-analysis

Hernandez, C. et al. Pre-operative Predictive Factors of Post-operative Pain in Patients With Hip or Knee Arthroplasty: A Systematic Review. *Reumatol Clin.* 11. 361-80. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review (37 studies). To analyze pre-surgical predictive factors of post-surgical pain in patients undergoing hip or knee arthroplasty. Databases: Medline, Embase and Cochrane Library.</p> <p>Search period: Inception - up to May 2013.</p> <p>Inclusion Criteria: Patients undertaking knee and/or hip arthroplasty, adults with moderate or severe pain (<math>\geq 4</math> on a Visual Analog Scale)</p>	<p>Population: Adult patients in whom total hip arthroplasty (THA) and/or total knee arthroplasty (TKA) was indicated.</p> <p>Intervention: Exposure to risk factors: preoperative predictive or determining factors for postoperative pain such as: age, sex, level of education, socioeconomic status, race, profession, underlying disease (type, duration, etc.), comorbidity, body mass index (BMI), level of self-care ability, quality of life, preoperative pain level (intensity, duration, etc.), surgeonrelated factors (age, sex, experience), waiting list, type of hospital, expectations, depression, anxiety, etc</p> <p>Comparison: Non-exposure to risk factors:</p>	<p>Primary: postoperative pain.</p> <p>Secondary: -</p> <p>Results: Study overview: 37 articles of moderate quality were selected. The articles included representative patients undergoing a knee or hip arthroplasty in our country; most of them were aged 60 years or above, with osteoarthritis, and with a high rate of obesity and comorbidities. Results: Only summary displayed due to length: We found great variability regarding the type of studies and predictive factors. There was a strong association between post-surgical pain and the following pre-surgical factors: female gender, low socio-economic status, higher pain, comorbidities, low back pain, poor functional status, and psychological factors (depression, anxiety or catastrophic pain). Conclusions: There are pre-surgical factors that might influence post-surgical pain in patients undergoing a knee or hip arthroplasty.</p> <p>Author's Conclusion: "In conclusion, once the indication for THA and/or TKA is clear, it is essential to take into account certain preoperative variables that influence the outcome of the intervention as far as postoperative pain is concerned. Nonmodifiable variables, such as female sex, younger patient age, low socioeconomic status and the presence of</p>	<p>37 articles included (see full text)</p>

in whom predictive factors of post-surgical pain were evaluated before surgery. Systematic reviews, meta-analyses, controlled trials and observational studies were selected.

**Exclusion Criteria:**  
Animals and basic science articles, reviews of prosthesis, prosthesis due to fractures, patients with rheumatic diseases or studies with mixed population in which disaggregated data was not possible to obtain.

comorbidities, should be taken into account when deciding on the indication for arthroplasty. Modifiable variables or those amenable to intervention, such as obesity, the presence of intense preoperative pain or severe functional impairment, and the existence of psychological disturbances, should be evaluated systematically to assess the performance of preoperative interventions that contribute to the achievement of better outcomes with THA and TKA."

**Methodical Notes**

**Funding Sources:** The present article was funded by MSD. MSD did not participate in choosing the subject, in the development of the review or the conclusions, or in the writing of the article.

**COI:** Fees from MSD in payment for scientific work. Fees from Myers Squibb, Grunenthal, MSD, Pfizer and Zambón in payment for teaching activities, as consultancy fees or as funding for research projects.

**Study Quality:** The two reviewers extracted the data from the selected studies using specific templates predesigned for this review. To evaluate the methodological quality of the studies included, they used the Oxford quality scale. In general, the quality was moderate and even high in some of them. Many articles scored in the range of 2 on the Oxford scale.

**Heterogeneity:** No meta-analysis was performed due to high heterogeneity.

**Publication Bias:** Publication bias not investigated.

**Notes:**  
Oxford level of evidence: Systematic review

**Hinrichs-Rocker, A. et al. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) - a systematic review. Eur J Pain. 13. 719-30. 2009**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review (50 studies)</p> <p>Databases: PubMed, PsychINFO, Embase, and Cochrane Databases.</p> <p>Search period: 1996 and June 2006.</p> <p>Inclusion Criteria: Relevant studies were defined as those exploring prediction, risk factors, correlates, and incidence of Chronic post-surgical pain (CPSP). Other inclusion criteria were: studies of surgical patients, with English or German abstracts, published between January 1996 and June 2006, on adult human subjects, with minimum 3 months follow-up, and pain lasting at least 3 months.</p>	<p>Population: Any surgery</p> <p>Intervention: Exposure to psychosocial risk factors.</p> <p>Comparison: Non-exposure to psychosocial risk factors.</p>	<p>Primary: Chronic post-surgical pain.</p> <p>Secondary: -</p> <p>Results: Study population: 149 articles were identified as potentially relevant and screened for psychosocial predictors/correlates for CPSP. Of the 149 potentially relevant articles, 36 considered psychosocial predictors/correlates in an adequate manner. 14 additional studies were identified from screening the reference lists of primary articles and relevant reviews. Each of the 50 relevant studies was rated in terms of its level of evidence, and respective score points were awarded. 13 papers were classified as level of evidence A1 (score points = 4), 3 papers as a level of evidence A2 (score points = 3), 26 as a level of evidence B1 (score points = 2), 7 as a level of evidence B2 (score points = 1), and 1 paper as a level of evidence C (score points = 0).</p> <p>Results: The grade of association between chronic post-surgical pain and each psychosocial predictor/correlate implicated in these studies was then assessed using these scores. Only summary displayed here due to length (rest see article).</p> <p>Depression, psychological vulnerability, stress, and late return to work showed likely correlation with CPSP (grade</p>	<p>49 studies included, see full article.</p>

**Exclusion Criteria:** Studies without original data, case reports with fewer than 20 patients, and studies of pre-operative pain only. In addition, we documented characteristics such as study, participant, intervention, and outcome measure types, as recommended by The Cochrane Collaboration (2006).

of association = 1). Other factors were determined to have either unlikely (grade of association = 3) or inconclusive (grade of association = 2) correlations. In addition, results were examined in light of the type of surgery undergone. The incidence of chronic pain ranged from 9% to 70%.

**Author's Conclusion:** "The present review was designed with the development of the psychosocial component of an assessment instrument for risk factors of CPSP in mind. Certainly, a complete screening instrument should assess biomedical risk factors as well. We realize that our results are quite preliminary, since the evidence for most factors is weak and heterogeneous. Further studies will be necessary to validate these predictors and to better characterize the influence of different types of surgery on CPSP outcomes."

**Methodical Notes**

**Funding Sources:** "The authors are grateful to the Else Kröner-Fresenius-Stiftung (Germany) for supporting this research."

**COI:** none specified.

**Study Quality:** We evaluated psychosocial predictors or correlates of post-operative pain across all studies. First, the level of evidence of each study was determined (A1, A2, B1, B2, C and D) using the characteristics of study type, number of subjects, and completeness of followup. For ease of comparison, the level of evidence was translated into score points from 0 to 4 (see Appendix A). Increasing score point values reflect a higher level of evidence. For each predictor/correlate, the grade of association with CPSP was determined using the score points from all available studies. A grade of association of 1 represents a likely association between a particular factor and CPSP. It was awarded when at least 3 studies investigated this predictor/correlate and the sum score of studies favoring an association was at least double that of the sum score of studies showing no association with CPSP.

**Heterogeneity:** No applicable. No meta-analysis was performed.

**Publication Bias:** not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic review  
Downgrade to evidence level 2.

No evaluation of risk of bias. Author's mention of study quality does not investigate risk of bias, also no individual results are not displayed. The associations and their strength is based upon this evaluated quality.

**Khatib, Y. et al. Do Psychological Factors Predict Poor Outcome in Patients Undergoing TKA? A Systematic Review. Clin Orthop Relat Res. 473. 2630-8. 2015**

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p><b>Study type:</b> Systematic review: (19 studies) Whether (1) psychological factors, as measured by preoperative self-reported questionnaires, predicted poor outcome after TKA, and (2) whether certain psychological factors examined predicted poor outcome better than others</p> <p><b>Databases:</b> MEDLINE, CINAHL, EMBASE, and PsycINFO databases, augmented with a manual search of bibliographies.</p> <p><b>Search period:</b> Inception to October 2013.</p> <p><b>Inclusion Criteria:</b> -Prospective studies in adults undergoing joint replacement surgery -a measurement of a preoperative psychological factor such as anxiety or depression, and evaluated with at least one reliable and validated self-reporting instrument. -at least one reliable and valid clinical measurement tool assessing patient-reported or objectively measured knee function before and after TKA. -comparison of the clinical outcomes, specifically, patient satisfaction, pain, and/or function after TKA, based on preoperatively measured psychological factors.</p>	<p><b>Population:</b> Adults undergoing joint replacement surgery (TKA).</p> <p><b>Intervention:</b> Exposure to risk factors (preoperative psychological factors such as anxiety or depression).</p> <p><b>Comparison:</b> Non-exposure to risk factors.</p>	<p><b>Primary:</b> relation of baseline mental health factors with postoperative patient dissatisfaction. The dissatisfaction rate was recorded or calculated from the study where possible. Dissatisfaction was defined as any patient who reported being unhappy or unsure about the benefit from the TKA at least 6 months after surgery.</p> <p><b>Secondary:</b> relationships of baseline mental health factors with postoperative patient pain and function levels as reported on knee-scoring tools. The magnitude of effect of baseline mental health on postoperative pain and function was recorded.</p> <p><b>Results:</b> Study population: A total of 19 studies (17 cohort studies and two cross-sectional surveys) containing data on 9046 TKAs performed in 8704 adult patients were included in the review. Mean patient age was 68 years and followup ranged from 6 to 60 months (mean study followup, 14 months). Clinical and methodologic heterogeneity in study design prevented the statistical pooling of data and subsequent meta-analysis. Results: only summary results displayed here due to length, rest see full article. Dissatisfaction rates with TKA ranged from</p>	<p>Ayers, Blackburn, Brander, Brander, Ellis, Engel, Escobar, Gandhi, Heck, Jones, Judge, Kim, Lingard &amp; Riddle, Papkostidou, Riddle, Scott, Smith &amp; Zautra, Sullivan, Wyld</p>

-minimum followup of 6 months was required. The minimum time was chosen owing to evidence indicating that improvement at 6 months has been shown to be an approximation for improvement at 12 months and 24 months. Studies that reported results of TKA together with other types of replacement surgery, including THA or unicompartmental knee arthroplasty, were included if the data for TKA outcomes could be isolated. No restriction was placed on language or publication date and a translation service was used for studies published in languages other than English if required.

**Exclusion Criteria:** Retrospective studies were excluded owing to the risk of recall bias in determining psychological status. In the case of duplicate publications or publications that used the same set of patient data, only the most complete paper was included, or the first publication if patient numbers were identical.

7.5% to 28.3%. Psychological health was deemed a significant predictor of satisfaction, pain, or function at a minimum of 6 months after TKA in 16 studies. The remaining three studies did not find this relationship. Baseline mental health factors may affect patient satisfaction, their long-term perception of pain, and their motivation to return to the desired level of function. We were unable to determine the most relevant psychological states or the most appropriate way to assess them with our systematic review.

**Author's Conclusion:** A patient dissatisfaction rate of up to 28% after TKA is high and must be addressed. Preexisting psychological factors may be treatable, thus possibly altering patient outcome after surgery. A form of preoperative psychological assessment may be beneficial in understanding patients' expectations and influence patient selection, education, and the timing of surgery. Future research should focus on identifying the main mental health states or psychological factors that influence postsurgical outcomes and ways to measure the prevalence and severity of such states in patients considered suitable candidates for TKA.

**Methodical Notes**

**Funding Sources:** Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

**COI:** "Conflict of Interest Forms for authors and Clinical Orthopaedics and Related Research<sup>1</sup> editors and board members are on file with the publication and can be viewed on request."

**Study Quality:** Included studies were assessed for quality according to the Newcastle-Ottawa scale. Two reviewers independently performed the search, identified eligible studies, assessed their methodologic quality, and extracted data

**Heterogeneity:** Not applicable, not meta-analysis was performed.

**Publication Bias:** Publication bias not investigated.

**Notes:**  
Oxford level of evidence: 1 Systematic review:

Lesin, M. et al. Factors associated with postoperative pain and analgesic consumption in ophthalmic surgery: a systematic review. *Surv Ophthalmol.* **60.** 196-203. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review (12 studies)</p> <p>Databases: Medline, Scopus, PsycINFO and CINAHL. A forward search was performed in Web of Science to identify additional citations that may have been missed through electronic database searching methods. Finally, the reference lists of included manuscripts were read to find relevant citations.</p>	<p><b>Population:</b> Adults (18 years or older) of both sexes undergoing any kind of ophthalmic surgery.</p> <p><b>Intervention:</b> Exposure to risk factors.</p> <p><b>Comparison:</b> Non-Exposure to risk factors.</p>	<p><b>Primary:</b> Postoperative pain intensity</p> <p><b>Secondary:</b> Analgesic consumption.</p> <p><b>Results:</b> included studies: 12 studies with 1,515 participants. The median number of patients in the included studies was 59.</p> <p><b>Results:</b> Only summary, due to length and number of risk factors, rest see article.</p> <p>Female sex, longer duration of surgical procedure, second eye surgery as a consecutive procedure, type of surgery, general anesthesia, lower satisfaction with anesthesia, and postoperative nausea may contribute to increased postoperative pain intensity. Type of surgery, type of anesthesia, and patient satisfaction with anesthesia were associated with increased analgesic consumption.</p> <p><b>Author's Conclusion:</b> Based on our experience and our review of the literature, pain in ophthalmic surgery is often under-recognized. One of the problems may be the division of patient care in clinical departments. Surgeons operate on the patient; anesthesiologists manage the anesthesia and analgesia in the operating room. Nurses are more available to patients, but may not be trained to ask uncomplaining patients about pain. Considering the well-known</p>	<p>12 studies included: Abramoff 2001, Aslan 2013, Benatar-Haserfaty 2013, Fekrat 2001, Fung 2005, Henzler 2004, Itaya 1995, Koay 1992, Nolan 1987, Schaffer 1988, Torres 2007, Waterman 1998.</p>

<p><b>Search period:</b> Inception - October 2013.</p> <p><b>Inclusion Criteria:</b> We included any type of study reporting factors associated with postoperative pain and analgesic consumption in ophthalmic surgery. We included studies that recruited adults (18 years or older) of both sexes undergoing any kind of ophthalmic surgery.</p> <p><b>Exclusion Criteria:</b> We excluded reports and interventional studies reporting the effectiveness of analgesics and anesthetics, as well as studies on phantom eye pain.</p>	<p>negative consequences of untreated pain, ophthalmic pain is important because understanding the associated factors may help us to alleviate it, improve patient outcomes, and reduce medical costs. Age is an especially pertinent issue, although the included studies that did not have biased patient selection did not show an age-related differences in ophthalmic postoperative pain. In other fields there is conflicting data regarding age and pain intensity, some showing greater pain sensitivity in younger, and others in older people.</p> <p>A numeric rating scale is the preferred pain intensity scale across different age groups, and visual analogue scales should not be used in elderly patients.</p> <p>The influence of sex has been intensively studied, although its role in pain sensitivity is still unclear. Evidence of physiological or hormonal factors that may contribute to sex differences in pain sensitivity has not been found or is inconsistent. Sex differences were not confirmed in the three out of four included studies that addressed this issue.</p> <p>Longer duration of surgery may be associated with more intense pain. Longer surgical times may produce more extensive tissue damage or indicate a more difficult operation. One striking finding is an association between general anesthesia and more severe postoperative ophthalmic pain. After general anesthesia the effect of the anesthetic quickly disappears, whereas local anesthesia has a prolonged duration at the surgical site, especially when using regional blocks or long-acting anesthetics such as bupivacaine. Comparing pain intensity immediately after surgical procedures may be misleading.</p> <p>In addition, some of the studies included in this systematic review assessed surgical procedures that are no longer widely used, such as extracapsular cataract surgery that requires an incision in the surgical limbus of approximately 10 mm and causes more damage to sensory stimuli and fiber nociceptors than phacoemulsification, in which the incision is less than 3 mm.</p>	
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<p><b>Methodical Notes</b></p>
<p><b>Funding Sources:</b> none declared.</p> <p><b>COI:</b> None of the authors has any proprietary/ financial interest to disclose.</p> <p><b>Study Quality:</b> Risk of bias in the included studies was assessed using a modified Cochrane Risk of Bias tool. "One study described as randomized did not have a single feature of a randomized controlled trial so has a high risk of bias.2 Another study was a randomized controlled trial with allocation concealment;40 the method of randomization was not described, however. All outcomes were reported, but details of how the allocations were concealed from participants, personnel, and outcome assessors were not provided. No other sources of bias were detected. Ten included studies were observational, without blinding of the participants or outcome assessors, so all studies had a high risk of bias in relation to allocation concealment. On the other hand, all studies were judged to have a low risk of bias from selective outcome reporting. All studies reported outcome data of interest, but some without specifying the statistical tests used. Unclear or high risk of bias was present in all studies for both "comparability of groups" and "other risk of biases" domains."</p> <p><b>Heterogeneity:</b> Not applicable. Meta-analysis was not possible because of the degree of heterogeneity in included studies (age of patients, ophthalmic procedures, follow-up time, factors analyzed). Therefore, qualitative data synthesis was conducted.</p> <p><b>Publication Bias:</b> not investigated.</p> <p><b>Notes:</b> Oxford level of evidence: 1 Systematic review Risk of bias evaluated but individual results are not displayed.</p>

<p>Tolver, M. A. et al. Early pain after laparoscopic inguinal hernia repair. A qualitative systematic review. <i>Acta Anaesthesiol Scand.</i> <b>56.</b> 549-57. 2012</p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review (71 studies)</p> <p>Databases: Pubmed, Embase, CINAHL, and the Cochrane database.</p> <p>Characterise pain within the first post-operative week after transabdominal</p>	<p>Population: Patients undergoing transabdominal preperitoneal hernia repair (TAPP) and total extraperitoneal hernia repair (TEP).</p> <p>Intervention:</p>	<p>Primary: First post-operative week pain</p> <p>Secondary: -</p> <p>Results: Study overview: A total of 71 papers including 14,023 patients undergoing laparoscopic groin hernia repair were identified (Fig. 1). The 71 papers consisted of 44 RCTs, 23 prospective trials, and four retrospective trials. The 44 RCTs consisted of 14 trials of ideal quality, 16 trials of moderate quality, and 14 trials of low quality.</p> <p>Results: only summary results available due to length: Post-operative pain is most severe on day 0 and mainly on a level of 13–58 mm on a visual analogue scale and decreases to low levels</p>	<p>71 articles included, see full text.</p>

<p>preperitoneal repair (TAPP) and total extraperitoneal repair (TEP), and to identify patient-related predictors of early pain.</p> <p>Search period: January 1990 to October 2011.</p> <p>Inclusion Criteria: "Papers in English, details on pain in humans during the first 7 days after TAPP and/or TEP, and age ≥ 18 years. Papers published as Epub ahead of print were included."</p> <p>Exclusion Criteria: not specified.</p>	<p>Exposure to risk factors (none specified).</p> <p>Comparison: Non-exposure to risk factors.</p>	<p>on day 3. There seems to be no difference in pain intensity and duration when TEP and TAPP are compared. Deep abdominal pain (i.e. groin pain/visceral pain) dominates over superficial pain (i.e. somatic pain) and shoulder pain (i.e. referred pain) after TAPP. Predictors of early pain are young age and pre-operative high pain response to experimental heat stimulation. Furthermore, evidence supported early pain intensity as a predictive risk factor of chronic pain after laparoscopic groin hernia repair.</p> <p>Author's Conclusion: In conclusion, early pain after laparoscopic groin hernia repair is comparable to pre-operative levels as early as post-operative day 3, and deep abdominal pain dominates over incisional pain and shoulder pain. Young age and pre-operative high pain response are predictive factors for early postoperative pain intensity. Future studies are necessary to evaluate gender as a possible risk factor and the effect of various surgical and analgesic interventions, so the early post-operative period can be optimised, convalescence shortened, and the risk of chronic pain reduced.</p>	
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<p><b>Methodical Notes</b></p>
<p><b>Funding Sources:</b> Financial support was obtained from Region Zealand's research fund (RESUS), Denmark</p> <p><b>COI:</b> Travel/accommodation expenses for international meetings covered by Baxter Healthcare. Expert testimony from Baxter Healthcare support from Johnson &amp; Johnson, Covidien, and Baxter Healthcare and has had travel/ accommodation expenses for international meetings covered by Baxter Healthcare.</p> <p><b>Study Quality:</b> Randomised controlled trials (RCT), prospective, and retrospective studies were included if they met the inclusion criteria. RCTs were evaluated by quality assessment (one assessor) as described in details elsewhere. The assessment included 11 questions about stated aim, control group, statistics, randomisation process, defined study end point, unbiased assessment, description of the intervention and adequate follow-up. Each trial was then categorised into three quality groups: A = ideal quality, B = moderate quality, and C = poor quality. Evidence levels were categorised on the classification described by Eccles et al. (Ia-IV), where Ia equals highest evidence level, and IV equals lowest evidence level. "The 44 RCTs consisted of 14 trials of ideal quality, 16 trials of moderate quality, and 14 trials of low quality."</p> <p><b>Heterogeneity:</b> Not applicable, no meta-analysis was performed.</p> <p><b>Publication Bias:</b> not investigated.</p> <p><b>Notes:</b>  Oxford level of evidence: 1 Systematic review  Downgraded to evidence level 2:  Missing study descriptives, missing results for the study quality assesment. No specified list of risk factors or outcomes (other than early pain).</p>

<p><b>Wang, L. et al. Predictors of persistent pain after breast cancer surgery: a systematic review and meta-analysis of observational studies. Cmaj. 188. E352-e361. 2016</b></p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 2</p> <p>Study type: Systematic review and meta-analysis (30 studies)  We conducted a systematic review and meta-analysis of observational studies to explore factors associated with persistent pain among women who have</p>	<p>Population: Breast cancer surgery patients</p> <p>Intervention: Exposure to risk factors</p> <p>Comparison: Non-exposure to risk factors.</p>	<p>Primary: persistent postoperative pain.</p> <p>Secondary: -</p> <p>Results: 30 studies, involving a total of 19813 patients, reported the association of 77 independent variables with persistent pain. High-quality evidence showed increased odds of persistent pain with younger age (OR for every 10-yr decrement 1.36, 95% confidence interval [CI] 1.24–1.48), radiotherapy (OR 1.35, 95% CI 1.16–1.57), axillary lymph node dissection (OR 2.41, 95% CI 1.73–3.35) and greater acute postoperative pain (OR for every 1 cm on a 10-cm visual analogue scale 1.16, 95% CI 1.03–1.30). Moderate-quality evidence suggested an association with the presence of preoperative pain (OR 1.29, 95% CI 1.01–1.64). Given the 30% risk of pain in the absence of risk factors, the absolute risk increase corresponding to these ORs ranged from 3% (acute postoperative pain) to 21% (axillary lymph node dissection). High-quality evidence showed no association with body mass index, type of breast surgery, chemotherapy or endocrine therapy.</p>	<p>30 articles, see full text.</p>



<p>undergone surgery for breast cancer.</p> <p>Databases: MEDLINE, Embase, CINAHL and PsycINFO databases</p> <p>Search period: from inception to Mar. 12, 2015</p> <p>Inclusion Criteria: Cohort or case-control studies that explored the association between risk factors and persistent pain (lasting ≥ 2 mo) after breast cancer surgery.</p> <p>Exclusion Criteria: -</p>	<p><b>Author's Conclusion:</b> Development of persistent pain after breast cancer surgery was associated with younger age, radiotherapy, axillary lymph node dissection, greater acute postoperative pain and preoperative pain. Axillary lymph node dissection provided the only high-yield target for a modifiable risk factor, and no single nonmodifiable risk factor changed risk sufficiently to define a target population for an intervention to prevent persistent pain. Future research should establish the association between overall comorbidity, radiotherapy dosage and persistent postsurgical pain, and determine whether axillary nerve-sparing techniques are effective for reducing chronic pain after breast surgery.</p>
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<p><b>Methodical Notes</b></p> <p><b>Funding Sources:</b> No funds were received for the preparation of this manuscript. Li Wang is supported by a Michael G. DeGroote Postdoctoral Fellowship. The funding organization had no role in the design and conduct of the study; in the collection, analysis or interpretation of the data; or in the preparation, review or approval of the manuscript.</p> <p><b>COI:</b> None declared.</p> <p><b>Study Quality:</b> We used criteria from Users' Guides to the Medical Literature to assess risk of bias, including representativeness of the study population, validity of outcome assessment, loss to follow-up and whether predictive models were optimally adjusted. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the quality of evidence for all meta-analyses.</p> <p><b>Heterogeneity:</b> "We evaluated heterogeneity for all pooled estimates through visual inspection of forest plots,<sup>27</sup> because statistical tests of heterogeneity can be misleading when sample sizes are large and CIs are therefore narrow."</p> <p><b>Publication Bias:</b> We detected no evidence of publication bias (symmetric funnel plot; Begg test p = 0.3; Egger test p = 0.2 funnel plots available by request to the authors).</p> <p><b>Notes:</b>  Oxford level of evidence: 1 Systematic review and meta-analysis  Downgraded to EL 2 due to several reasons:  Lacking description of endpoints and predictors. Absence of label describing the individual studies and their characteristics, quality assessments etc.  Heterogeneity was only evaluated by visual inspection, not statistical methods. Authors reported funnel plots, but did not display them in the article.</p>
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<p><b>Wylde, V. et al. Post-operative patient-related risk factors for chronic pain after total knee replacement: a systematic review. BMJ Open. 7. e018105. 2017</b></p>			
Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
<p>Evidence level: 1</p> <p>Study type: Systematic review (14 included studies)</p> <p>Patient-related risk factors for chronic pain after total knee replacement.</p>	<p>Population: Adults undergoing primary TKR predominantly for osteoarthritis: Studies that included patients with TKR combined with patients undergoing</p>	<p>Primary: Severity of pain in the replaced knee measured with a patient-reported outcome measure at 6 months or longer after TKR surgery (chronic pain).</p> <p>Secondary: adverse events and other aspects of pain recommended by the core outcome set for chronic pain after TKR. These included pain interference with daily living, pain and physical functioning, temporal aspects of pain, pain description, emotional aspects of pain, use of pain medication and satisfaction with pain relief.</p> <p>Results: Included studies: Of the 14 included studies, three were from the UK, two each from Australia, USA and Spain, and one study from Belgium, Denmark, France, Portugal and Serbia. Thirteen studies were conducted at a single centre and one study did not report the number of centres. Eleven of</p>	<p>14 included studies: Crosbie 2010, Edwards 2009, Pinot 2013, Phillips 2014, Veal 2015, Grosu 2016, Sayers 2016, Thomazeau</p>

<p>Databases: MEDLINE, Embase and PsycINFO.</p> <p>Search period: Inception to 17 October 2016.</p> <p>Inclusion Criteria: Cohort studies that have explored the relationships between factors measured in the first 3 months postoperative and longer term pain outcomes. Adults undergoing TKR with risk exposure or and postoperative pain severity at 6 months.</p> <p>Exclusion Criteria: Studies that used a composite pain and function measure to assess outcome.</p>	<p>other orthopaedic procedures were included if separate results were available for patients with TKR.</p> <p>Intervention: Exposure: Postoperative patient-related risk factors measured in the first 3 months after surgery: Patients with exposure were those with a risk factor (categorical variable) or higher level of risk factor (continuous variable). The focus of this</p> <p>Comparison: Patients with absence of risk factor (categorical variable) or lower level of risk factor (continuous variable).</p>	<p>the studies were cohort studies, two were randomised controlled trials retrospectively analysed as cohort studies and one was a case-control study with prospective data collection. Sample sizes ranged from 23 to 402, with a median of 115 participants.</p> <p>Results: only main outcomes reported, due to length: Acute postoperative knee pain 8 studies including data from 737 participants evaluated the association between pain in the first 3 months after TKR and chronic pain. Timing of acute postoperative pain was classified as pain within the first postoperative week; pain between 1 and 2 weeks postoperatively; and pain from 2 weeks to 3 months. Pain as a risk factor was assessed using the VAS (3 studies), VDS (2 studies), NRS (two studies), WOMAC Pain Scale (1 study) and PainDETECT (1 study). 5 studies conducted multivariable analysis, two studies conducted univariable analysis, and for one study no statistical analysis was performed as data were provided by authors on a small subset of patients with TKR.</p> <p>Pain severity on postoperative days 1–7 4 studies with data from 491 participants evaluated whether pain severity in the first week after surgery was associated with chronic pain. 2 were at risk of bias due to missing data and one study was at risk of bias due to inadequate consideration of confounding. Methods used to assess pain included the VDS, VAS and NRS. 3 studies found that more severe acute postoperative pain was associated with more severe pain at 6–12 months after TKR, although in one study this association was attenuated completely after adjustment for preoperative pain. One study found no association between pain at 42 hours after surgery and the presence of chronic pain at 4–6 months.</p> <p>Pain severity in postoperative days 8–14 3 studies with data from 191 participants evaluated whether pain severity on postoperative days 8–14 was associated with chronic pain. One study was at risk of bias due to missing data and two studies were at risk of bias due to inadequate consideration of confounding. Pain was assessed in two studies with the VDS and in one with the WOMAC Pain Scale and VAS. Pain on postoperative day 8 and at 2 weeks was not found to be associated with chronic pain in two studies, and descriptive data only were available for the study that evaluated pain on postoperative day 10. In the study with low risk of bias apart from with regard to representativeness, pain severity at 2 weeks was not found to be associated with pain at 6 months after TKR.</p> <p>Pain severity between 2 weeks and 3 months postoperatively 5 studies with data from 314 participants evaluated whether pain severity between 2 weeks and 3 months postoperatively was associated with chronic pain after TKR. Two studies were at risk of bias due to missing data and three studies were at risk of bias due to inadequate consideration of confounding. Methods to assess pain were the WOMAC Pain Scale, VAS and VDS. In one study with risk of bias associated only with conduct at a single centre, pain severity at 8 weeks postoperatively was found to be associated with pain at 6 months postoperatively when assessed with the WOMAC but not the VAS. In one study with univariable analysis, pain severity assessed on day 30 was found to be associated with pain severity at 6 months but not 12 months after TKR. The same study found that pain at 3 months postoperatively was not associated with pain severity at 6 months and 12 months postoperatively. In another study, neuropathic pain at 6 weeks postoperatively was found to be moderately associated with pain at 39–51 months after surgery. In one study, there was no difference in pain at 12 months in patients with different average pain levels at 6 weeks. However considering ‘worst’ pain, 7/14 patients with moderate to severe pain at 6 weeks reported moderate to severe pain at 12 months compared with 1/9 patients with none or mild pain at 6 weeks. A study that assessed global pain and night pain at 1 month and 3 months postoperatively found that they were associated with global pain and night pain, respectively, at a future time point (6 months and 12 months).</p> <p>Author's Conclusion: "In conclusion, this systematic review found insufficient evidence to draw conclusions about the association between any postoperative patient-related factor and chronic pain after TKR. To complement this research, systematic reviews are ongoing to evaluate the effectiveness of preoperative, perioperative and postoperative interventions in preventing chronic pain after TKR (PROSPERO reference CRD42017041382). Further highquality research is required to provide robust evidence on postoperative risk factors, and inform the development and evaluation of targeted interventions to optimise patients' outcomes after TKR."</p>	<p>2016, Elson an Brenkel 2006, Nunez 2007, Nunez 2009, Crosbie 2010, Riis 2014, Kocic 2015</p>
<p><b>Methodical Notes</b></p>			
<p><b>Funding Sources:</b> This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research (RP-PG-0613-20001). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The funder had no role in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for</p>			

publication.

COI: None declared.

**Study Quality:** We developed a non-summative checklist for use in this review. This checklist consisted of four items to assess selection bias (inclusion of consecutive patients and representativeness), bias due to missing data (follow-up rates) and bias due to inadequate consideration of confounding (multivariable or univariable analysis). These items were informed by existing tools, including the MINORs, Newcastle-Ottawa Quality Assessment Scale and the ROBINS-I tool. Each item was rated as adequate, not adequate or not reported.

"Eight studies reported that consecutive patients were recruited, eight studies followed up >80% participants, and nine studies conducted multivariable analysis. All studies had issues relating to selection bias because none were reported as being conducted at multiple centres."

**Heterogeneity:** not applicable, no meta-analysis was performed.

"Meta-analysis was not possible due to heterogeneity in the assessment of risk factors and outcomes."

**Publication Bias:** not investigated.

**Notes:**

Oxford level of evidence: 1 Systematic review