National Institute for Health and Care Excellence

Consultation

Perioperative care in adults

[N2] Evidence review for managing acute postoperative pain

NICE guideline

Appendices

November 2019

Draft for consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

1

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

1

Simple Analgesics: Paracetamol

Appendix A: Review protocols

Table 1: Review protocol: Oral paracetamol vs intravenous paracetamol

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	What is the most clinically and cost effective strategy for managing acute postoperative pain?
2.	Review question	What is the most clinically and cost effective strategy for managing acute postoperative pain? There are six topic areas that have been identified: Paracetamol routes of delivery Non-steroidal anti-inflammatory drugs (NSAIDs) Opioid administration strategy (Continuous epidural ,intravenous PCA, spinal) Opioid post-operative administration strategy (oral vs iv) Ketamine Neuropathic nerve stabilisers This protocol addresses, 'what is the clinical and cost effectiveness of IV paracetamol compared to oral paracetamol given post operatively in managing acute postoperative pain?'
3.	Objective	To determine which paracetamol administration strategy is clinically and cost effective in managing acute post-operative pain.
4.	Searches	The following databases will be searched: • Embase • MEDLINE • The Cochrane Library Searches will be restricted by: • English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in

		the final review.
5.	Condition or domain being studied	What is the most clinically and cost effective strategy for managing acute postoperative pain
6.	Population	Inclusion: Adults (18 years and older) who have undergone surgery. Exclusion: People who have had Surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	IV paracetamol
8.	Comparator/Reference standard/Confounding factors	Oral paracetamol
9.	Types of study to be included	Randomised controlled trials and systematic reviews of randomised controlled trials
10.	Other exclusion criteria	Non-English language Cross-over randomised controlled trials
11.	Context	NA

12.	Primary outcomes (critical outcomes)	• Health-related quality of life
		• Pain reduction
		  ○ < 6 hours post op
		  ○ 6 hours- 24 hours post op
		Pain reduction measured by:
		• patient reported pain (physician, nurse or carer reported pain will not be included);
		• patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both)
		• patient reported pain intensity expressed hourly over four to six hours using validated pain scales, or reported summed pain intensity difference (SPID) at four to six hours
		• Number of participants achieving at least 50% pain relief
		• Time to achieve 50% pain intensity
		• Amount of additional medication use (rescue medication)
		  ○ < 6 hours post op
		  ○ 6 hours- 24 hours post op
		• Time to rescue medication
		• Adverse events (including respiratory depression, nausea, vomiting)

13.	Secondary outcomes (important outcomes)	• Psychological distress and mental well-being • Symptom scores • Functional measures

		• Length of stay in intensive care • Length of stay in hospital • Hospital readmission The committee agreed that a difference of 1 (10%) on a 10 point pain scale such as NRS or VRS indicated a clinically important difference. For the remaining outcomes, the committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Cochrane RoB (2.0) will be used to assess intervention reviews 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management The clinical approach to this area of the scope is multimodal. The pain management approach for each patient will depend on many factors

		and include the procedure and the severity of pain. For this reason it is not meaningful to compare the drugs listed in the topic areas to each other. There isn't an overall question evaluating which drug is the most effective and a network meta-analysis is not appropriate.			
17.	Analysis of sub-groups	Subgroups: • people aged over 60 years • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation • American Society of Anesthesiologists (ASA) Physical Status grade			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	NA			
22.	Anticipated completion date	NA			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☑
		Piloting of the study selection process		☐	☑
		Formal screening of search results against eligibility criteria		☐	☑
		Data extraction		☐	☑
		Risk of bias (quality) assessment		☐	☑
		Data analysis		☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail			

		perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swaine Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis Ms Lina Gulhane
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	NA

30.	Reference/URL for published protocol	NA	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • Issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Perioperative care Pain relief Paracetamol	
33.	Details of existing review of same topic by same authors	NA	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	NA	
36.	Details of final publication	www.nice.org.uk	

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2 **Table 2: Review protocol: Intravenous paracetamol and intravenous opioid**

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	What is the most clinically and cost effective strategy for managing acute postoperative pain?
2.	Review question	What is the most clinically and cost effective strategy for managing acute postoperative pain? There are six topic areas that have been identified: Paracetamol routes of delivery Non-steroidal anti-inflammatory drugs (NSAIDs) Opioid administration strategy (Continuous epidural ,intravenous PCA, spinal) Opioid post-operative administration strategy

		(oral vs iv) Ketamine Neuropathic nerve stabilisers This protocol addresses, 'What is the clinical and cost effectiveness of IV paracetamol given intraoperatively in managing acute post-operative pain?'
3.	Objective	To determine if adding iv paracetamol to iv opioids is clinically and cost effective in managing acute postoperative pain?
4.	Searches	The following databases will be searched: • Embase • MEDLINE • The Cochrane Library Searches will be restricted by: • English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	What is the most clinically and cost effective strategy for managing acute postoperative pain
6.	Population	Inclusion: Adults (18 years and older) who have undergone surgery. Exclusion: People who have had Surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	IV paracetamol and IV opioids
8.	Comparator/Reference standard/Confounding factors	IV opioids (and placebo)
9.	Types of study to be included	Randomised controlled trials and systematic reviews of randomised controlled trials
10.	Other exclusion criteria	Non-English language Cross-over randomised controlled trials
11.	Context	NA
12.	Primary outcomes (critical outcomes)	• Health-related quality of life • Pain reduction o < 6 hours post op o 6 hours- 24 hours post op Pain reduction measured by: • patient reported pain (physician, nurse

		or carer reported pain will not be included); • patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both) • patient reported pain intensity expressed hourly over four to six hours using validated pain scales, or reported summed pain intensity difference (SPID) at four to six hours • Number of participants achieving at least 50% pain relief • Time to achieve 50% pain intensity • Amount of additional medication use (rescue medication) o < 6 hours post op o 6 hours- 24 hours post op • Time to rescue medication • Adverse events (including respiratory depression, nausea, vomiting)
13.	Secondary outcomes (important outcomes)	• Psychological distress and mental well-being • Symptom scores • Functional measures • Length of stay in intensive care • Length of stay in hospital • Hospital readmission The committee agreed that a difference of 1 (10%) on a 10 point pain scale such as NRS or VRS indicated a clinically important difference. For the remaining outcomes, the committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.

		Cochrane RoB (2.0) will be used to assess intervention reviews 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management The clinical approach to this area of the scope is multimodal. The pain management approach for each patient will depend on many factors and include the procedure and the severity of pain. For this reason it is not meaningful to compare the drugs listed in the topic areas to each other. There isn't an overall question evaluating which drug is the most effective and a network meta-analysis is not appropriate.	
17.	Analysis of sub-groups	Subgroups: • people aged over 60 years • opioid tolerant populations • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation • American Society of Anesthesiologists (ASA) Physical Status grade	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	NA		
22.	Anticipated completion date	NA		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swaine Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis Ms Lina Gulhane		

26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details	NA	
30.	Reference/URL for published protocol	NA	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • Issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Perioperative care Pain relief Paracetamol	
33.	Details of existing review of same topic by same authors	NA	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published

		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	NA	
36.	Details of final publication	www.nice.org.uk	

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2 **Table 3: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[788] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies

	excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. For example, economic evaluations based on observational studies will be excluded, when the clinical review is only looking for RCTs,

Appendix B: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of paracetamol

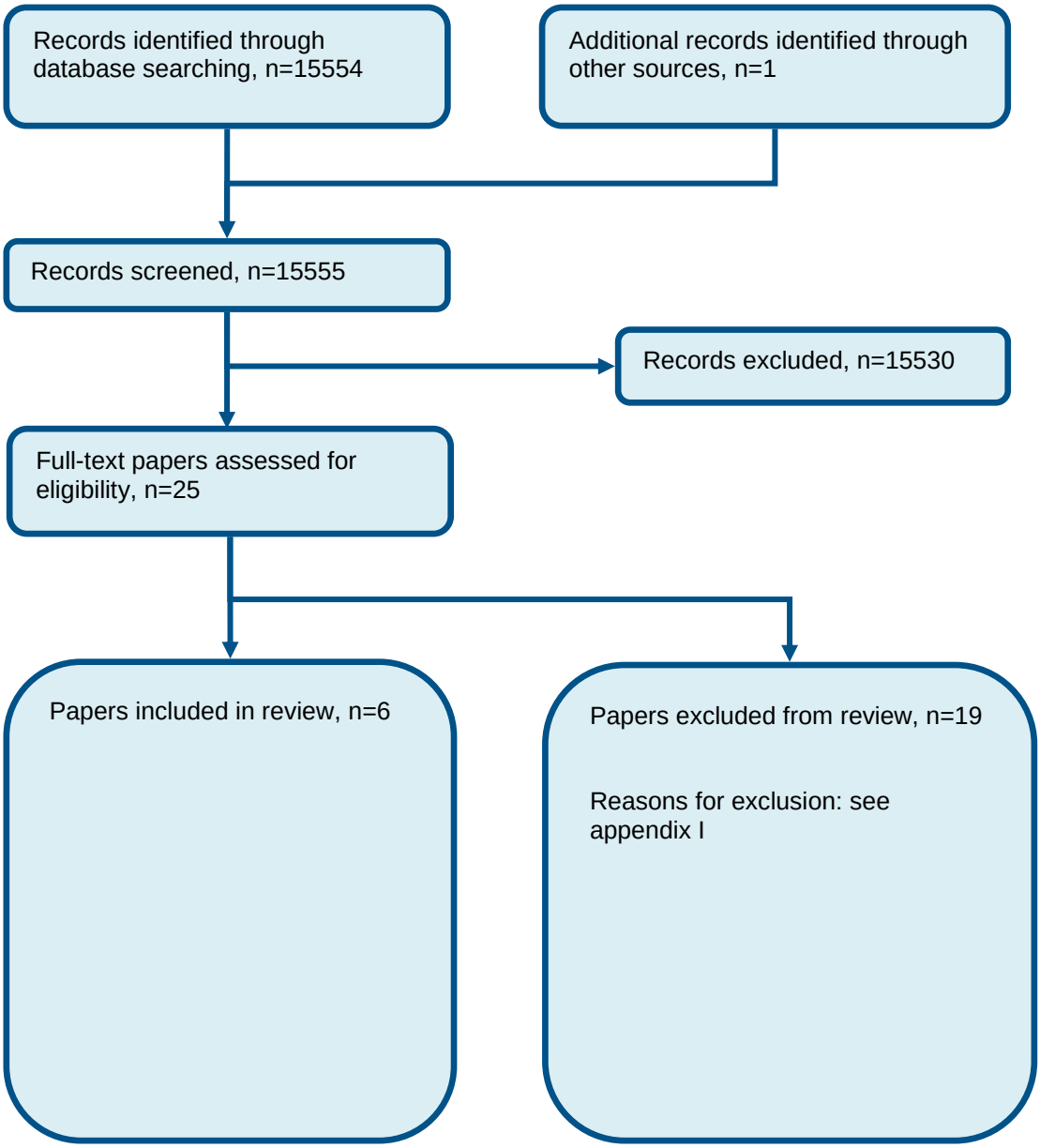
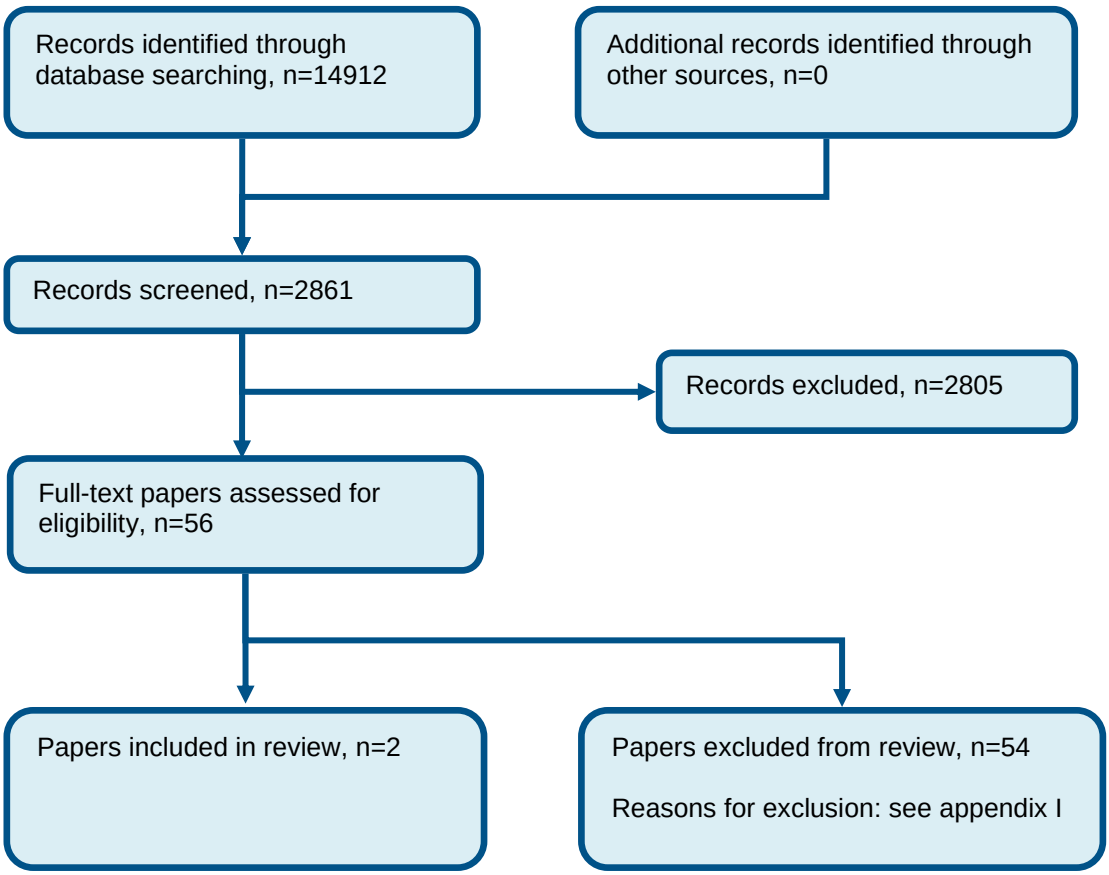


Figure 2: Flow chart of clinical study selection for the review of intravenous paracetamol and intravenous opioid



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Appendix C: Clinical evidence tables

C.1 Paracetamol

Study	Fenlon 2013[293]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=130)
Countries and setting	Conducted in United Kingdom; Setting: Maxillofacial day ward in general hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 1 hour
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: wisdom teeth removal
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18–65 undergoing at least one lower third molar extraction under general anaesthesia as a day case
Exclusion criteria	Had taken analgesic medication in the preceding 24 hours or caffeine in the preceding 6 hours, could not swallow tablets, had allergy to any of the trial medications, previous liver or renal dysfunction, were pregnant or breastfeeding, or had a history of drug or alcohol abuse.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Range: IV:18.7-54.4 Oral:18.1-57.7. Gender (27:47): Ethnicity: NA Not reported
Further population details	Not recorded
Indirectness of population	No indirectness
Interventions	(n=65) Intervention 1: IV paracetamol. i.v. paracetamol (Perfalgan TM) (plus oral placebo). Duration 1 hour. Concurrent medication/care: None reported . Indirectness: Serious indirectness; Indirectness comment: paracetamol given intraoperatively after induction of anaesthesia. (n=65) Intervention 2: Oral paracetamol. oral 1g paracetamol (plus IV placebo). Duration 1 hour. Concurrent medication/care: none stated . Indirectness: Serious indirectness; Indirectness comment: paracetamol given

Study	Fenlon 2013[293]
	intraoperatively after induction of anaesthesia.
Funding	Academic or government funding (National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0408-16304).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PARACETAMOL versus ORAL PARACETAMOL

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: satisfactory pain relief at 1 hour at 1 hour; Group 1: 17/65, Group 2: 15/63
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ;
Group 1 Number missing: 2, Reason: Did not receive allocated intervention (non-protocol general anaesthesia)
Group 2 Number missing: 0
- Actual outcome: pain score at < 6-24 hours; Group 1: mean 4.7 VAS (SD 2.2); n=63, Group 2: mean 5.2 VAS (SD 2.2); n=65; VAS 0-100mm Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Didn't receive allocated intervention anaesethesia; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: number of patients requesting rescue medication at 1 hour; Group 1: 9/63, Group 2: 18/65; Comments: Rescue medication = 50mg IV diclofenac
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Didn't receive allocated intervention anaesethesia; Group 2 Number missing: 0
-
Actual outcome: Time to rescue medication at 1 hour;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Didn't receive allocated intervention anaesethesia; Group 2 Number missing: 0
median scores in minutes
IV:57.2 min (95% CI:55.4, 59.2) PO: 54.3 min (95% CI: 51.2, 57.4) Kaplan-Meier survival analysis log-rank test P=0.066

Study	Fenlon 2013[293]
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Jarde 1997[439]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=214)
Countries and setting	Conducted in France; Setting: Nord Hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inpatients aged 18–75 years, scheduled for hallux valgus plasty performed with local anaesthesia under standardized local anaesthesia.
Exclusion criteria	Patients with a known hypersensitivity or intolerance to paracetamol, severely impaired hepatic function, pain other than that caused by the current surgery, history of drug or alcohol dependence.
Recruitment/selection of patients	sequential patients
Age, gender and ethnicity	Age - Mean (SD): IV bolus: 52.2 (13); oral: 51.7 (14.5) . Gender (M:F): 22:192. Ethnicity: not recorded
Further population details	Not reported
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=108) Intervention 1: IV propacetamol 2g [= paracetamol (PA) 1g] plus placebo oral tablet. Duration 6 hours postoperative. Concurrent medication/care: Standard anaesthesia bupivacaine Indirectness: No indirectness (n=50) Intervention 2: Oral paracetamol 1g plus placebo IV. Duration 6 hours postoperative. Concurrent medication/care: Standard anaesthesia bupivacaine. Indirectness: No indirectness

Study	Jarde 1997[439]
Funding	Equipment / drugs provided by industry (The study was supported by a grant from Bristol–Myers Squibb.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PROPACETAMOL BOLUS versus ORAL PARACETAMOL Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain intensity at 6 hours (SPID6); group 1 -43.19 (359.34), n=108, group 2: -153.57 (415.55), n=106 Risk of bias: All domain - High, Selection - High, Blinding - low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea; Group 1: 0/108, Group 2: 1/106; Comments: Risk of bias: All domain - High, Selection - High, Blinding - low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: vomiting; Group 1: 1/108, Group 2: 1/106 Risk of bias: All domain - High, Selection - High, Blinding - low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: time to remedication -Actual outcome: time to remedication: People with paracetamol (oral) remedicated earlier than did those treated with propacetamol (IV). Risk of bias: All domain - High, Selection - High, Blinding - low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Moller 2005[741]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=150)
Countries and setting	Conducted in Denmark; Setting: university hospital

Study	Moller 2005[741]
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: patients for removal of an impacted mandibular third molar (and ipsilateral maxillary third molar if indicated) under standardized local anaesthesia and suffered moderate to severe pain (assessed on a four-point scale) within 4 hours of surgery
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inpatients aged 18–50 years, ASA I or II, scheduled for ipsilateral maxillary third molar if indicated) under standardized local anaesthesia, moderate to severe pain (assessed on a four-point scale) within 4 h of surgery.
Exclusion criteria	pregnant or breast-feeding women, alcohol or drug abuse, psychiatric or medical disorder able to modify patient compliance, history of non-responsiveness to acetaminophen or ibuprofen, hypersensitivity to acetaminophen,NSAIDs or local anaesthetic, gastric or peptic ulcer, IBD,blood coagulation abnormalities, pancreatic disease, impaired liver or kidney function. No analgesia 12hours before or 5 hours after study drug, No paracetamol in previous 30 days.
Recruitment/selection of patients	sequential patients
Age, gender and ethnicity	Age - Mean (range): IV bolus:25.6(20-42) IV infusion: 24.2 (18-39) oral:23.8 (19-36) . Gender (M:F): 61:90. Ethnicity: not recorded
Further population details	Not reported
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: IV paracetamol. 2g Propacetamol bolus injection (over 2 minutes) Duration 4 hours post-operative . Concurrent medication/care: Prilocain 3% and felypressin 0.54µg ml-1 (3.6-7.6ml) local anaesthesia Indirectness: No indirectness (n=50) Intervention 2: IV paracetamol. IV propacetamol iv infusion . Duration 4 hours postoperative . Concurrent medication/care: Prilocain 3% and felypressin 0.54µg ml-1 (3.6-7.6ml) local anaesthesia. Indirectness: No indirectness (n=50) Intervention 3: Oral paracetamol. oral acetaminophen 1 g

Study	Moller 2005[741]
	#Duration 4 hours post-operative . Concurrent medication/care: Prilocain 3% and felypressin 0.54µg ml-1 (3.6-7.6ml) local anaesthesia. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (The study was supported by a grant from Bristol–Myers Squibb.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PROPACETAMOL BOLUS versus ORAL PARACETAMOL

Protocol outcome 1: Pain (< 6 hours post op)

- Actual outcome: Time to maximum pain relief at 6 hours;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
median scores bolus: 0.25 (0.25,0.27), oral:1.00 (0.73,1.00)

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Adverse events at 7 days; Group 1: 49/50, Group 2: 21/50; Comments: Patients with one or more AEs
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Adverse events: nausea at 7 days; Group 1: 13/50, Group 2: 0/50
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PROPACETAMOL INFUSION versus ORAL PARACETAMOL

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Maximum pain reduction from baseline at 6 hours;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Time to maximum pain relief at 6 hours;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
median scores Infusion:0.25 (0.27,0.48) versus oral:1.00 (0.73,1.00)

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Adverse events at 7 days; Group 1: 38/50, Group 2: 21/50; Comments: Patients with one or more AEs
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Moller 2005[741]
- Actual outcome: Adverse events:nausea at 7 days; Group 1: 9/50, Group 2: 0/50 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	O'Neal 2017[931]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=115)
Countries and setting	Conducted in USA; Setting: General hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 24 hours post surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: patients undergoing total knee arthroplasty under spinal anaesthesia
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adults 18 years and over undergoing unilateral total knee arthroscopy under spinal anaesthesia
Exclusion criteria	spinal anaesthesia failed, pregnant, weighed <50kgs,history of chronic opiate use, liver disease, known allergy or hypersensitivity to acetaminophen or opiates, dementia, alcohol abuse, renal impairment , or used acetaminophen 24 hours pre surgery.
Recruitment/selection of patients	unclear
Age, gender and ethnicity	Age - Mean (SD): IV group: 68(8.3) Oral group: 67 (9.0). Gender (M:F): 58:57. Ethnicity: not recorded
Further population details	Not reported
Extra comments	ASA physical status n (%) IV group I :3(5) II:40(70) III: 14 (25) Oral group I: 2(3)

Study	O'Neal 2017[931]
	II:43(74) III:12(23)
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: IV paracetamol. 1 g IV acetaminophen (and oral placebo) Duration Study medications were administered at the conclusion of surgery and before admission in the post anaesthesia care unit by the in-room anesthesia provider. Concurrent medication/care: Standard preoperative pain medication regimen included doses of celecoxib and OxyContin. Intraoperatively, all patients received a pericapsular injection of 300 mg ropivacaine, 30 mg ketorolac, 0.08 mg clonidine, and 1 mg epinephrine in a total volume of 100 cc of 0.9% sodium chloride 0.9% into the knee joint. In addition, a majority of patients received IV dexamethasone (4-10mg) intraoperatively at the discretion of the in-room anaesthesia provider before surgical incision. Indirectness: No indirectness (n=58) Intervention 2: Oral paracetamol. 1 g oral acetaminophen (and volume-matched IV normal saline (100 mL)). Duration Study medications were administered at the conclusion of surgery and before admission in the postanaesthesia care unit by the in-room anesthesia provider. Concurrent medication/care: Standard preoperative pain medication regimen included doses of celecoxib and OxyContin. Intraoperatively, all patients received a pericapsular injection of 300 mg ropivacaine, 30 mg ketorolac, 0.08 mg clonidine, and 1 mg epinephrine in a total volume of 100 cc of 0.9% sodium chloride 0.9% into the knee joint. In addition, a majority of patients received IV dexamethasone (4-10mg) intraoperatively at the discretion of the in-room anaesthesia provider before surgical incision. Indirectness: No indirectness
Funding	Academic or government funding (Pilot grant from Massachusettes General Hospital NIH awards :T32GM108554., F32HL134290)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV ACETAMINOPHEN versus ORAL ACETAMINOPHEN

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score in PACU at < 6 hours post op; Group 1: mean 0.56 NRS (0-10) (SD 0.99); n=57, Group 2: mean 0.67 NRS (0-11) (SD 1.2); n=58; NRS 0-11 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Age, sex, BMI, ASA physical status.

Study	O'Neal 2017[931]
Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: Opiate consumption at < 6 hours post op (IV hydromorphone equivalents in milligrams); Group 1: mean 0.47 mg (SD 0.56); n=57, Group 2: mean 0.54 mg (SD 0.53); n=58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, sex, BMI, ASA physical status. Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Opiate consumption at 24 hours post op (IV hydromorphone equivalents in milligrams);; Group 1: mean 1.25 mg (SD 1.3); n=57, Group 2: mean 1.49 mg (SD 1.34); n=58; Comments: Converted to IV hydromorphone equivalents in milligrams. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, sex, BMI, ASA physical status. Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Plunkett 2017[1007]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=67)
Countries and setting	Conducted in USA; Setting: Army medical centre
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: subjects with symptomatic cholelithiasis requiring laparoscopic cholecystectomy
Stratum	Overall

Study	Plunkett 2017[1007]
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients(18 years of age or older),symptomatic cholelithiasis , American Society of Anesthesiologist (ASA) rating of I–III, scheduled to undergo elective LapCholesectomy were eligible for inclusion.
Exclusion criteria	pregnancy, ASA rating IV-V, requires urgent surgery, chronic pain syndrome, prior abdominal operations or conversion from laparoscopic to open cholecystectomy, chronic liver or kidney disease, received intraoperative NSAIDs. NSAIDs, COX 2 agents or acetaminophen 24hours prior to surgery.
Recruitment/selection of patients	not recorded
Age, gender and ethnicity	Age - Mean (SD): IV:42.09 (12.42) Oral:37.07 (10.98). Gender (M:F): 9:51. Ethnicity: Non Hispanic white n=33 other n= 27
Further population details	not reported
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: IV paracetamol1,000 mg and oral placebo Duration 24 hours. Concurrent medication/care: Opioid (fentanyl and/or hydromorphone) analgesia intraoperatively. Narcotic analgesia perioperatively and narcotic rescue medication. Postoperative nausea and vomiting prophylaxis with dexamethasone, ondansetron or both.. Indirectness: No indirectness (n=33) Intervention 2: Oral paracetamol. 2x 1,000 mg oral acetaminophen(plus IV saline). Duration 24 hours. Concurrent medication/care: Opioid (fentanyl and/or hydromorphone) analgesia intraoperatively. Narcotic analgesia perioperatively and narcotic rescue medication. Postoperative nausea and vomiting prophylaxis with dexamethasone, ondansetron or both.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Cadence Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV ACETAMINOPHEN (PLUS ORAL PLACEBO) versus ORAL ACETAMINOPHEN (PLUS IV SALINE)

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain intensity difference from baseline at 24 hours (SPID24) Greater (and more positive) SPID24 scores reflect lesser pain intensity experienced

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Plunkett 2017[1007]
- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Adjusted mean IV:-69.69 (90% CI=-79.81- -59.57) OA: -63.96 (90% CI=-74.83 --53.09) mean difference 5.73 (90% CI -21.07 - 9.62). ANCOVA (F(1,550=0.39,P=0.54) (F(1,550 = 0.39, P =0.54). - Actual outcome: Pain scores 4 or more at 24 hours; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Binary logistic regression, β= 0.24, Exp(B) = 1.28, P =0.68),probability of reporting pain of 4 or higher, after adjusting for covariates, was slightly higher in the OA group (53.57%) than the IVA group (46.88%). Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Total opiate consumption (OME24) at 24 hours; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Adjusted mean IV:151.11 (90% CI 133.30-168.92) Oral:162.44 (90%CI 142.64-182.25) Mean difference 11.33 (90%CI -38.99-16.32) F(1,46)=0.47,P=0.50) (F(1,46) = 0.47, P = 0.50)	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Politi 2017[1009]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=120)
Countries and setting	Conducted in USA; Setting: hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 24 hours post surgery
Method of assessment of guideline condition	Surgery for primary hip or knee arthroplasty

1

Study	Politi 2017[1009]
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Any patient undergoing primary hip or knee arthroplasty over a 10-week period.
Exclusion criteria	Known hypersensitivity, hepatic impairment, or known liver disease.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Not reported
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Type of surgery:
Extra comments	None stated .
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: IV paracetamol. IV 1g acetaminophen preoperatively and every 6 hours post operatively for 2 hours Duration 24 hours post operative. Concurrent medication/care: The standard pain regimen included preoperative Celebrex 400mg, oxycontin 10 mg, and anti nausea medication. Intraoperatively,patients received decadron 10 mg, tranexamic acid 10 mg/kg, injection of 0.25% bupivacaine, with epinephrine into the retinaculum and/or arthrotomy repair site.Immediately postoperatively, IV dilaudid q2hr prn, oxycodone 5 mg prn, oxycontin 10mg q12x2 doses, a second dose of decadron 10 mg at 24 hours,Celebrex 200 mg daily and antinausea medication. Patients were discharged on percocet 5/325 mg prn and meloxicam 7.5 mg daily. Aspirin was typically used for deep vein thrombosis prophylaxis unless risk factors required Lovenox. (n=57) Intervention 2: Oral paracetamol. oral 1g acetaminophen preoperatively and then postoperatively every 6 hours for 24 hours . Duration 24 hours post operative. Concurrent medication/care: The standard pain regimen included preoperative Celebrex 400mg, oxycontin 10 mg, and anti nausea medication. Intraoperatively,patients received decadron 10 mg, tranexamic acid 10 mg/kg, injection of 0.25% bupivacaine, with epinephrine into the retinaculum and/or arthrotomy repair site.Immediately postoperatively, IV dilaudid q2hr prn, oxycodone 5 mg prn, oxycontin 10mg q12x2 doses, a second dose of decadron 10 mg at 24 hours,Celebrex 200 mg daily and antinausea medication. Patients were discharged on percocet 5/325 mg prn and meloxicam 7.5 mg daily. Aspirin was typically used for deep vein thrombosis prophylaxis unless risk factors required Lovenox.

Study	Politi 2017[1009]
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV ACETAMINOPHEN versus ORAL ACETAMINOPHEN

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain scores at 4 hours ;
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain post op scores IV:3.375 PO:4.402(P=0.33); Group 1 Number missing: 0; Group 2 Number missing: 0
Pain scores at 4 hours (change scores): IV:-0.561 PO:-1.012(P=0.32)

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain scores at 24 hours ;
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain post op scores IV:3.375 PO:4.402(P=0.33); Group 1 Number missing: 0; Group 2 Number missing: 0
Pain scores at 24 hours (change scores): IV:-0.795 PO:-1.058(P=0.11)

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Narcotic use (hydromorphone equivalents) at 4 hours ;
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain post op scores IV:3.375 PO:4.402(P=0.33); Group 1 Number missing: 0; Group 2 Number missing: 0

Mean: IV : 0.646, oral:0.678 p=0.866

Protocol outcome 4: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Narcotic use (hydromorphone equivalents) at 24 hours ;
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain post op scores IV:3.375 PO:4.402(P=0.33); Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Narcotic use (hydromorphone equivalents) at total consumption;
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Very high,

Study	Politi 2017[1009]
Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Pain post op scores IV:3.375 PO:4.402(P=0.33); Group 1 Number missing: 0; Group 2 Number missing: 0 Mean: IV : 0.104, oral:0.078 p=0.661	
Protocol outcomes not reported by the study	Quality of life ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

C.2 Intravenous paracetamol and intravenous opioid

Study	Choudhuri 2011[182]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Unknown; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Written and informed consent was obtained from all. Patients aged 18–70 year scheduled for laparoscopic cholecystectomy, and classified as ASA physical status I or II were included.
Exclusion criteria	Patients with diagnostic laparoscopy, those having contraindications to paracetamol (allergy, liver disease) or to nonsteroidal anti-inflammatory drugs (NSAIDs) (esophagogastroduodenal disease, renal insufficiency, and abnormal coagulation) were excluded, as were those on treatment by steroids, NSAIDs, or opioids before surgery.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Fentanyl+paracetamol 56/16.5; Fentanyl 54/19.1. Gender (M:F): Fentanyl + paracetamol 28/12; Fentanyl 31/9. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA

Study	Choudhuri 2011[182]
	1-2). 3. Type of surgery: lower and upper GI (Laparoscopic cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Paracetamol (IV) and opioid (IV) - Paracetamol + opioid. Both groups received fentanyl during induction and IM diclofenac for pain relief every 8 hourly for 24 h after surgery. those in the fentanyl plus paracetamol group (Group P) received 100 mL of Paracetamol IV (Perfalgan 1 gm) just before induction. Duration intraoperative +24 hours post op. Concurrent medication/care: Patients received oral premedication, 5 mg Diazepam on the night before surgery. After the administration of oxygen, anesthesia was induced in both the groups with IV propofol (2 mg/kg), fentanyl (2 µg/ kg), and rocuronium (0.6 mg/kg). Anesthesia was maintained by 1–2% isoflurane in nitrous oxide and oxygen (ratio 2:1). The lungs were mechanically ventilated, and ventilation was adjusted to maintain end-expiratory CO2 between 34–36 mm Hg depending on the different stages of laparoscopy. Fentanyl was repeated in the dose of 1 µg/kg intraoperatively if both HR and NIBP increased >20% from baseline despite maintaining adequate depth of anesthesia.. Indirectness: No indirectness (n=40) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Both groups received fentanyl during induction and IM diclofenac for pain relief every 8 hourly for 24 h after surgery. Patients in the fentanyl group (Group F) received 100 mL of normal saline. Duration intraoperative+24 ours post op. Concurrent medication/care: Patients received oral premedication, 5 mg Diazepam on the night before surgery. After the administration of oxygen, anesthesia was induced in both the groups with IV propofol (2 mg/kg), fentanyl (2 µg/ kg), and rocuronium (0.6 mg/kg). Anesthesia was maintained by 1–2% isoflurane in nitrous oxide and oxygen (ratio 2:1). The lungs were mechanically ventilated, and ventilation was adjusted to maintain end-expiratory CO2 between 34–36 mm Hg depending on the different stages of laparoscopy. Fentanyl was repeated in the dose of 1 µg/kg intraoperatively if both HR and NIBP increased >20% from baseline despite maintaining adequate depth of anesthesia.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACETAMOL + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain scores (VAS) at 6 h post op; Group 1: mean 2.4 (SD 0.6); n=40, Group 2: mean 2.8 (SD 0.3); n=40
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: pain scores (VAS) at 24 h post op; Group 1: mean 2.4 (SD 0.7); n=40, Group 2: mean 2.3 (SD 0.4); n=40

Study	Choudhuri 2011[182]
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Number of patients requiring rescue analgesic in post operative period at post op; Mean; (p: <0.05), Comments: Fentanyl + paracetamol group - 13/40; Fentanyl group 14/40); Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 4: Length of hospital stay - Actual outcome: Length of hospital stay at post op; Group 1: mean 1.3 days (SD 0.8); n=40, Group 2: mean 1.2 days (SD 0.5); n=40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Quality of life; Amount of additional medication use (< 6 hours post op); Adverse events (including respiratory depression, nausea, vomiting); Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)); Symptom scores ; Functional measures ; Length of stay in intensive care unit; Hospital readmission

Study	Memis 2010[700]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Turkey; Setting: ICU
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	The local Research Ethics Committee approved the study, and written informed consent was obtained from all patients. Forty adult patients (N18 years of age) admitted to the ICU after complex major abdominal or pelvic surgery, who were expected to require 24-hour postoperative sedation and ventilation, were studied.

Study	Memis 2010[700]
Exclusion criteria	Exclusion criteria included known allergy or hypersensitivity or contraindication to opioids or paracetamol, impaired liver function (transaminases N twice upper limit), renal dysfunction (creatinine level, N2.0 mg/dL), uncontrolled chronic diseases, or known or suspected history of alcohol or drug abuse. Patients who were pregnant or breast-feeding were excluded. Patients were also excluded if they had received paracetamol within 8 hours, any analgesic drug within 12 hours, or corticosteroids within 7 days before administration of study medication.
Recruitment/selection of patients	not stated
Age, gender and ethnicity	Age - Mean (SD): Meredipine group 60 (9.5); Meredipine +paracetamol 59.8 (12.9). Gender (M:F): 24/16. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (major abdominal or pelvic surgery).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Paracetamol (IV) and opioid (IV) - Paracetamol + opioid. IV paracetamol 1 g every 6 hours (Perfalgan 10 mg/mL, 100 mL; Bristol-Myers Squibb, Itxassou, France) and IV meperidine . Duration 24 hours. Concurrent medication/care: intraoperative analgesia was provided by fentanyl alone and the dose was recorded. Muscle relaxation was achieved with rocuronium, and anesthesia was maintained with a sevoflurane, air, and oxygen mixture. No fentanyl was allowed within 30 minutes of skin closure, and after skin closure, sevoflurane was discontinued. Propofol was infused during the transfer but was stopped on arrival in the ICU. Analgesia was provided by fentanyl alone and the dose was recorded. Muscle relaxation was achieved with rocuronium, and anesthesia was maintained with a sevoflurane, air, and oxygen mixture. No fentanyl was allowed within 30 minutes of skin closure, and after skin closure, sevoflurane was discontinued. Propofol was infused during the transfer but was stopped on arrival in the ICU. . Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients received 100 mL of serum saline IV every 6 hours and IV meperidine (Aldolan, 100 mg/2 mL; Gerot Pharmazeutika GMbH, Vienna, Austria) (n = 20, group M). Duration 24 hours. Concurrent medication/care: intraoperative analgesia was provided by fentanyl alone and the dose was recorded. Muscle relaxation was achieved with rocuronium, and anesthesia was maintained with a sevoflurane, air, and oxygen mixture. No fentanyl was allowed within 30 minutes of skin closure, and after skin closure, sevoflurane was discontinued. Propofol was infused during the transfer but was stopped on arrival in the ICU. . Indirectness: No indirectness
Funding	Funding not stated

Study	Memis 2010[700]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACETAMOL + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain (BPS) at extubation at at extubation; Group 1: mean 2.5 n/a (SD 0.8); n=20, Group 2: mean 3.6 n/a (SD 1.2); n=20; BPS (Behavioral pain score) 1-4 Top=High is poor outcome; Comments: The BPS is a pain scale for sedated and ventilated patients exclusively and is based on the sum of 3 subscales: facial expression, upper limb movements, and compliance with mechanical ventilationEach subscale is scored from 1 (no response) to 4 (full response). Therefore, BPS scores range from 3 (no pain) to 12 (maximal pain) [6,7]. The BPS has a maximal acceptable pain score of 5 [8]. When BPS values were more than 4, meperidine, 1 mg/kg IV, was administered and noted in 2 groups.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain (VAS) at 24 h at 24 hours; Group 1: mean 2.4 (SD 0.55); n=20, Group 2: mean 2.64 n/a (SD 0.3); n=20; VAS 0 - 10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Additional Meperidine at within 24 hours after the surgery; Group 1: mean 76.75 mg (SD 18.2); n=20, Group 2: mean 198 mg (SD 66.4); n=20; Comments: When BPS values were more than 4, meperidine, 1 mg/kg IV, was administered and noted in 2 groups. After extubation, assessment of postoperative pain was made on the basis of
the visual analog score (VAS, were 0 cm = “no pain” and 10 cm = “worst pain imaginable”). When VAS values were more than 4, meperidine, 1 mg/kg IV, was administered and
noted in 2 groups. Meperidine need by each group within 24 hours was determined according to BPS and VAS.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Postoperative adverse events (nausea + vomiting) at 24 hours postoperatively; Group 1: 1/20, Group 2: 8/20; Comments: p<0.05
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 5: Length of hospital stay
- Actual outcome: length of stay at ICU at hours post operatively; Group 1: mean 26 hours (SD 4); n=20, Group 2: mean 27 hours (SD 3); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Study	Memis 2010[700]
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Appendix D: Forest plots

D.1 IV paracetamol versus oral paracetamol

Figure 3: Pain scores at ≤ 6hours

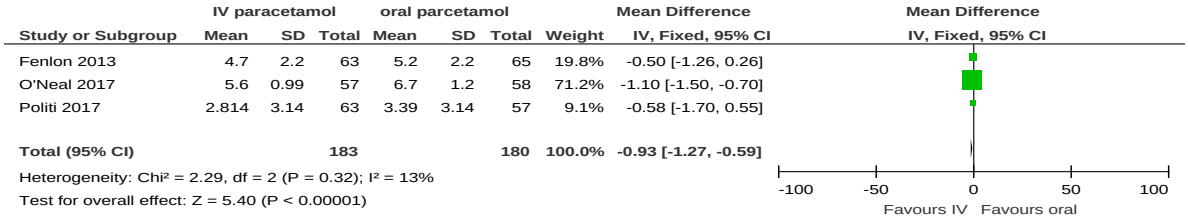


Figure 4: Pain score < 4 over 24 hours

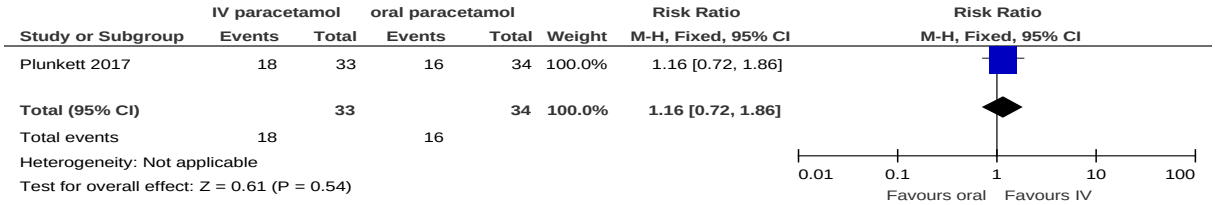


Figure 5: Pain score at 24 hours

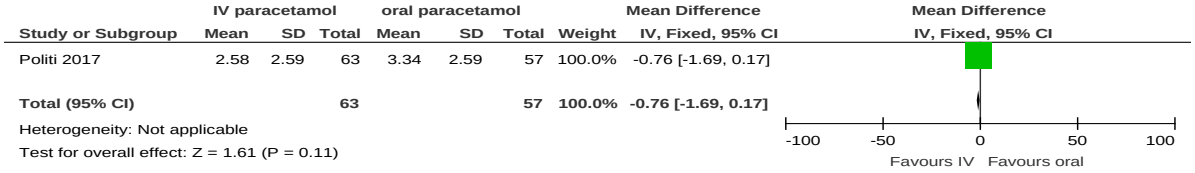


Figure 6: Summed pain intensity over 6 hours (SPID6)

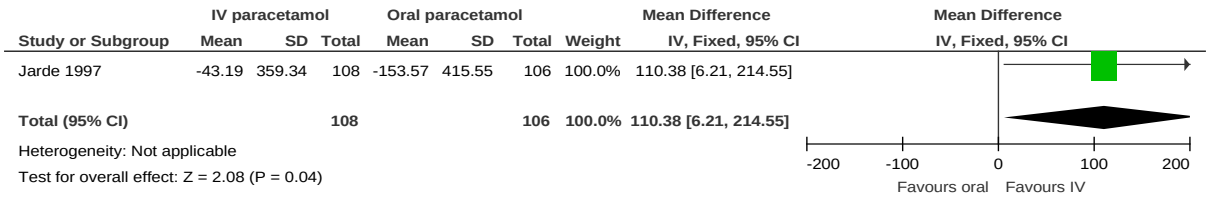


Figure 7: Summed pain intensity over 24 hours (SPID24)

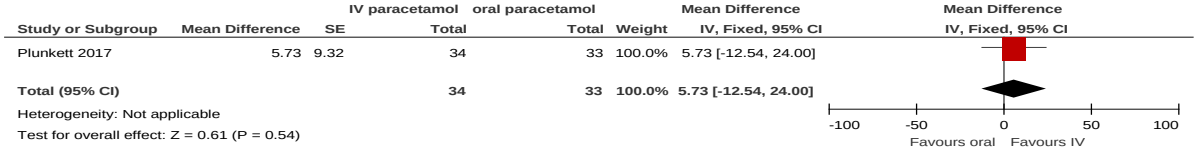
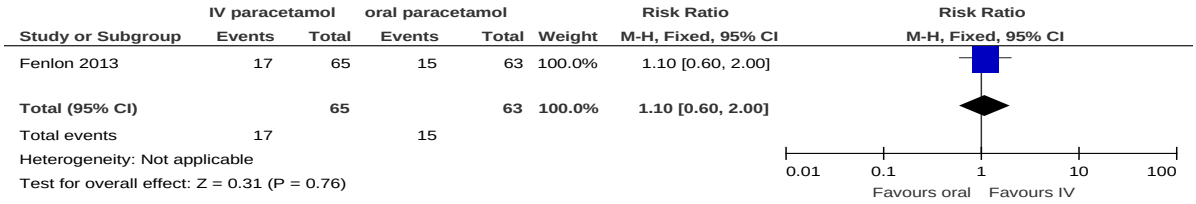


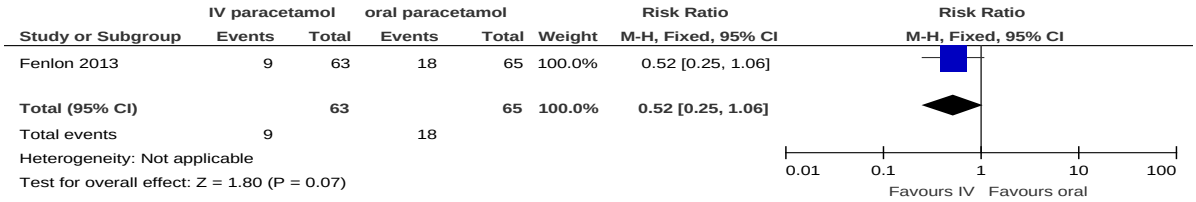
Figure 8: Satisfactory pain relief at 1 hour



1

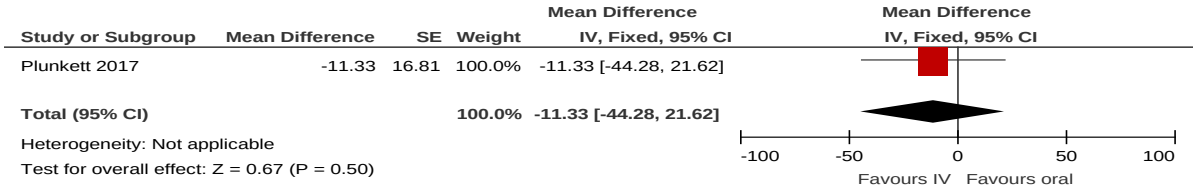
2 D.1.1 Rescue medicine

Figure 9: Number of patients requesting rescue medication at 1 hour (50mg iv diclofenac)



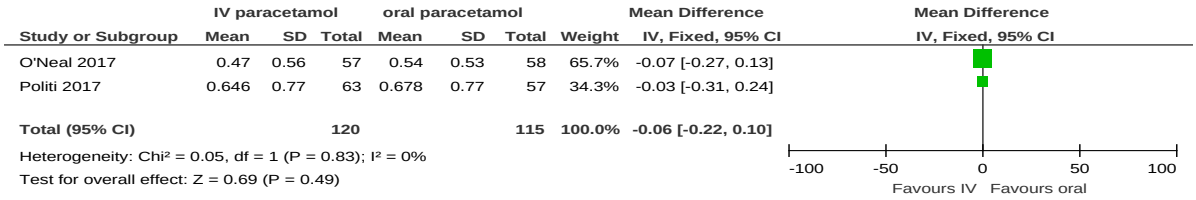
3

Figure 10: Total opiate consumption (OME24)



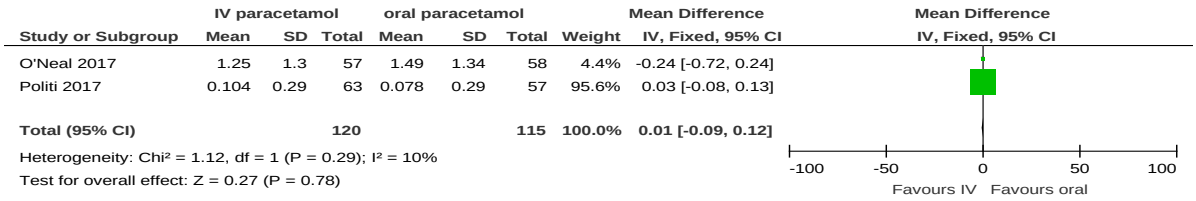
4

Figure 11: Opiate consumption (hydromorphine equivalents) <6 hours



5

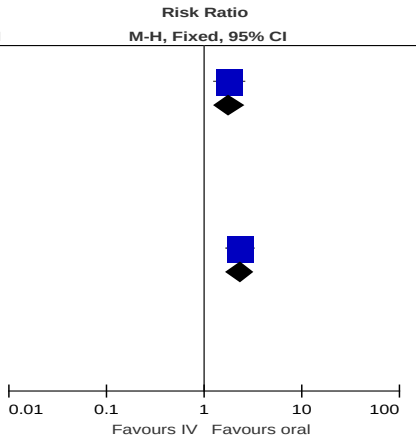
Figure 12: Opiate consumption (hydromorphine equivalents) >6-24 hours



6

Figure 13: Number of patients with > 1 adverse event

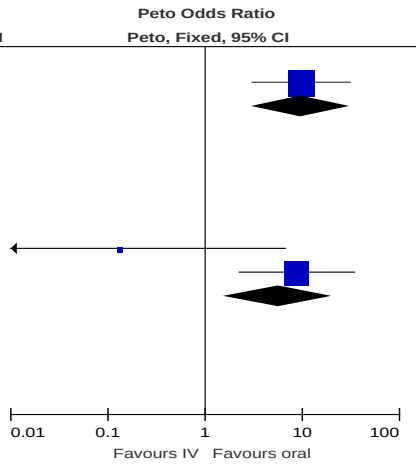
Study or Subgroup	IV paracetamol Events	Total	oral paracetamol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Infusion						
Moller 2005	38	50	21	50	100.0%	1.81 [1.26, 2.60]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**1.81 [1.26, 2.60]**
Total events	38		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.22 (P = 0.001)						
1.11.2 Bolus IV						
Moller 2005	49	50	21	50	100.0%	2.33 [1.68, 3.24]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**2.33 [1.68, 3.24]**
Total events	49		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.06 (P < 0.00001)						



1

Figure 14: Number of patients reporting nausea

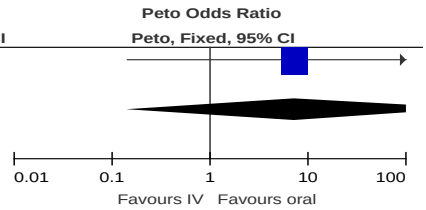
Study or Subgroup	IV paracetamol Events	Total	oral paracetamol Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.12.1 Infusion						
Moller 2005	13	50	0	50	100.0%	9.74 [3.05, 31.05]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**9.74 [3.05, 31.05]**
Total events	13		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.85 (P = 0.0001)						
1.12.2 Bolus						
Jarde 1997	0	108	1	106	10.8%	0.13 [0.00, 6.69]
Moller 2005	9	50	0	50	89.2%	8.81 [2.25, 34.42]
Subtotal (95% CI)		**158**		**156**	**100.0%**	**5.60 [1.55, 20.30]**
Total events	9		1			
Heterogeneity: Chi² = 3.92, df = 1 (P = 0.05); I² = 75%						
Test for overall effect: Z = 2.62 (P = 0.009)						



2

Figure 15: Number of patients reporting vomiting

Study or Subgroup	IV paracetamol Events	Total	Oral paracetamol Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Jarde 1997	1	108	0	106	100.0%	7.25 [0.14, 365.61]
Total (95% CI)		**108**		**106**	**100.0%**	**7.25 [0.14, 365.61]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						



3

D.2 IV paracetamol and IV opioid compared to IV opioid

Figure 16: Pain (BPS) at extubation

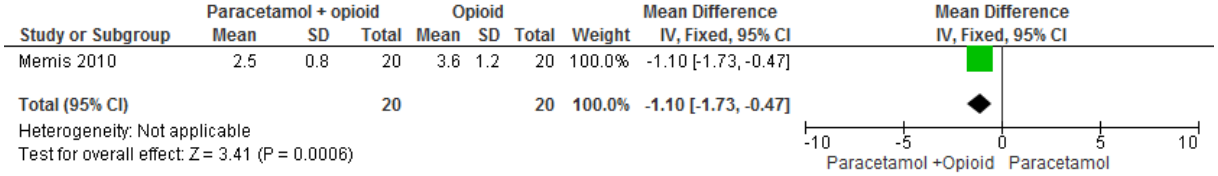


Figure 17: Pain (VAS) at 6 hours

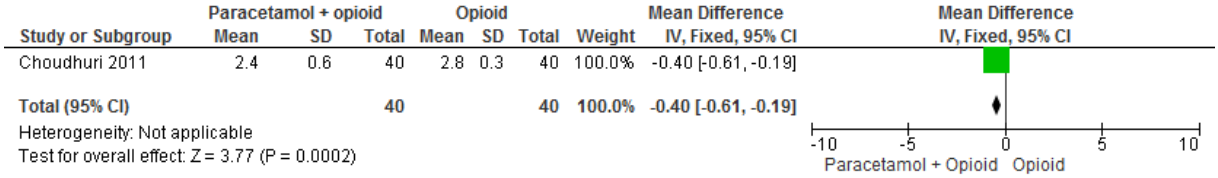


Figure 18: Pain (VAS) at 24 hours

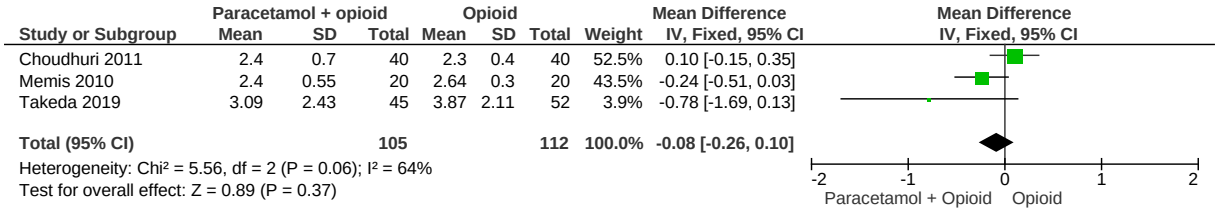


Figure 19: Amount of additional medication

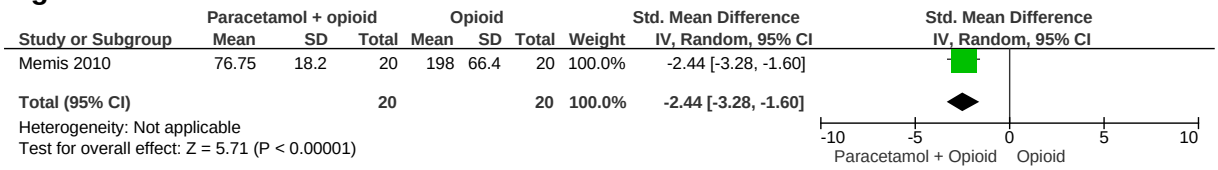


Figure 20: Total opioid consumption 24 hours

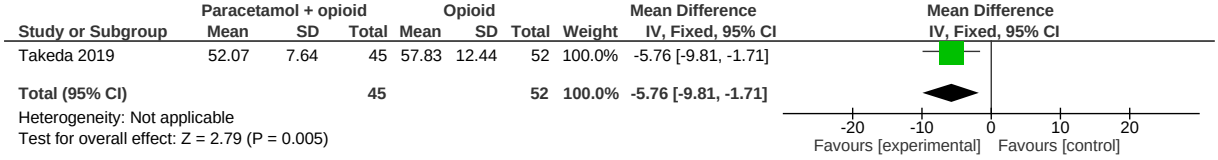


Figure 21: Adverse events

Figure 22: Length of stay at ICU

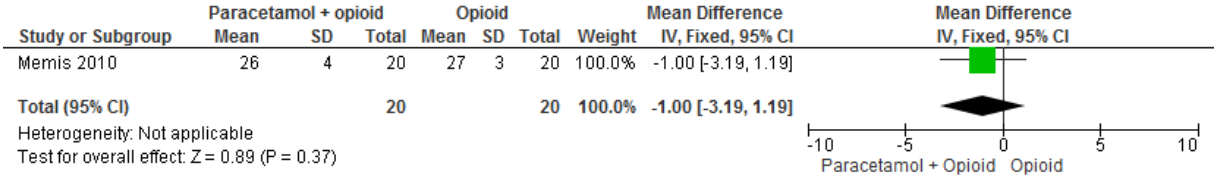
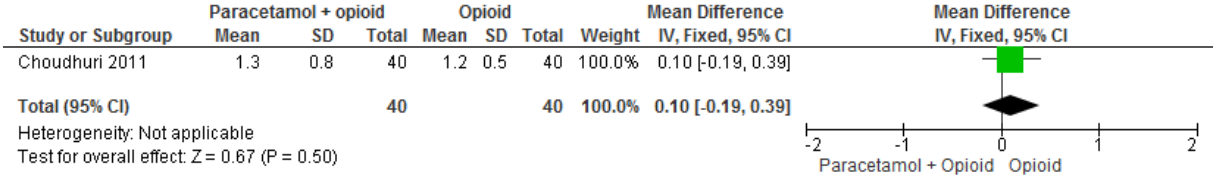


Figure 23: Length of hospital stay



Appendix E: GRADE tables

Table 4: Clinical evidence profile: IV paracetamol versus oral paracetamol for acute post-operative pain

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV paracetamol versus oral paracetamol	Control	Relative (95% CI)	Absolute		
Pain score at ≤6 hours (Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	183	180	-	MD 0.93 lower (1.27 to 0.59 lower)	⊕⊕OO LOW	CRITICAL
Pain score < 4 over 24 hours												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	18/33 (54.5%)	47.1%	RR 1.16 (0.72 to 1.86)	75 more per 1000 (from 132 fewer to 405 more)	⊕⊕OO LOW	CRITICAL
Pain score at 24 hours (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	63	57	-	MD 0.76 lower (1.69 lower to 0.17 higher)	⊕OOO VERY LOW	CRITICAL
Pain intensity at 6 hours (SPID6) (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	108	106	-	MD 110.38 higher (6.21 to 214.55 higher)	⊕OOO VERY LOW	CRITICAL
Pain intensity at 24 hours (SPID24) (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	34	33	-	MD 5.73 higher (12.54 lower to 24 higher)	⊕⊕OO LOW	CRITICAL

Satisfactory pain relief at 1 hour												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	17/65 (26.2%)	23.8%	RR 1.1 (0.6 to 2)	24 more per 1000 (from 95 fewer to 238 more)	⊕OOO VERY LOW	CRITICAL
Requesting rescue medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/63 (14.3%)	27.7%	RR 0.52 (0.25 to 1.06)	133 fewer per 1000 (from 208 fewer to 17 more)	⊕⊕OO LOW	CRITICAL
Total opiate consumption (OME24) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	34	33	-	MD 11.33 lower (44.28 lower to 21.62 higher)	⊕⊕OO LOW	CRITICAL
Opiate consumption (hydromorphine equivalents) <6 hours (Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	120	115	-	MD 0.06 lower (0.22 lower to 0.1 higher)	⊕⊕OO LOW	CRITICAL
Opiate consumption (hydromorphine equivalents) 6-24 hours (Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	120	115	-	MD 0.01 higher (0.09 lower to 0.12 higher)	⊕⊕OO LOW	CRITICAL
Number of participants with adverse events - Infusion												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/50 (76%)	42%	RR 1.81 (1.26 to 2.6)	340 more per 1000 (from 109 more to 672 more)	⊕⊕OO LOW	CRITICAL
Number of participants with adverse events - Bolus IV												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	49/50 (98%)	42%	RR 2.33 (1.68 to 3.24)	559 more per 1000 (from 286 more to 941 more)	⊕⊕OO LOW	CRITICAL
Nausea - Infusion												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/50 (26%)	0%	Peto Odds ratio 9.74 (3.05 to 31.05)	Not estimable	⊕⊕OO LOW	CRITICAL
Nausea - Bolus												
2	randomised trials	very serious[1]	very serious[4]	no serious indirectness	no serious imprecision	none	9/158 (5.7%)	0.64%	Peto Odds Ratio 5.6 (1.55 to 20.3)	3 more per 100 (from 0 more to 12 more)	⊕OOO VERY LOW	CRITICAL
Vomiting												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/108 (0.93%)	0%	Peto Odds Ratio 7.25 (0.14 to 365.61)	Not estimable	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 because the majority of the evidence included an indirect population or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes
[4] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis

Table 5: Clinical evidence profile: IV paracetamol and IV opioid compared to IV opioid

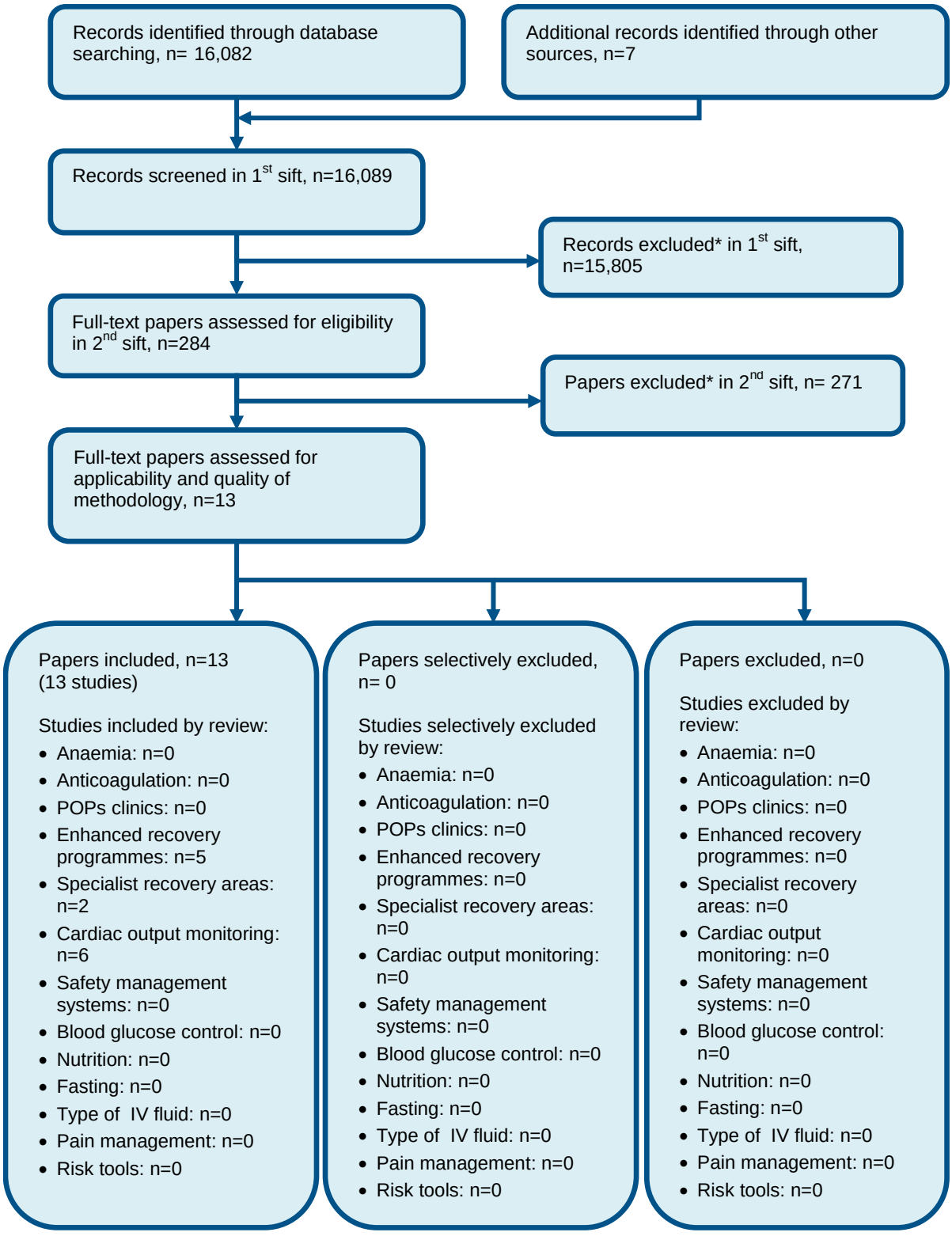
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Iv Paracetamol + iv Opioid**	**Iv Opioid**	**Relative (95% CI)**	**Absolute**		
Pain (BPS) at extubation (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	20	20	-	MD 1.1 lower (1.73 to 0.47 lower)	⊕⊕OO LOW	CRITICAL
Pain (VAS) at 24 h (follow-up mean 24 hours; Better indicated by lower values)												
3	randomised	serious[2]	serious[3]	no serious	very	none	105	112	-	MD 0.08 lower (0.26	⊕OOO	CRITICAL

	trials			indirectness	serious[1]					lower to 0.1 higher)	VERY LOW	
Amount of additional medication (Meperidine) 24 h post surgery (follow-up mean 24 hours; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	20	20	-	MD 121.25 lower (151.42 to 91.08 lower)	⊕⊕OO LOW	CRITICAL
Total opioid consumption (morphine equivalents) 24 h post-surgery												
1	Randomised trials	no serious indirectness	no serious inconsistency	no serious indirectness	serious	none	45	52		The mean total opioid consumption in the intervention groups was 5.76 lower (9.81 to 1.71 lower)	⊕⊕⊕⊖ MODERATE1 due to imprecision	CRITICAL
Adverse events (follow-up mean 24 hours)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	65	68	RR 0.26 (0.08 to 0.87)	130 fewer per 1000 (from 26 fewer to 162 fewer)	⊕⊕⊕O MODERATE	
Length of stay at ICU (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	60	60	-	MD 1 lower (3.19 lower to 1.19 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Pain (VAS) at 6h (follow-up mean 6 hours post operation; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	40	40	-	MD 0.4 lower (0.61 to 0.19 lower)	⊕OOO VERY LOW	
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	40	40	-	MD 0.1 higher (0.19 lower to 0.39 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded once if the majority of the evidence is from studies at high risk of bias. Downgraded twice if the majority of the evidence

Appendix F:Health economic evidence selection

Figure 24: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Health economic evidence tables

None.

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 6: Studies excluded from the clinical review of managing acute postoperative pain: opioid administration strategy

Study	Exclusion reason
Api 2009[42]	Inappropriate comparison. Incorrect interventions. IVparacetamol versus placebo
Matsuda 2017[683]	Commentary on Politi 2017
McNicol 2016[691]	Inappropriate comparison. Incorrect interventions. Analysis compared IV paracetamol and IV propacetamol with either placebo or an active comparator, which in turn could be an opioid, NSAID, or other analgesic.
NCT 2014[853]	Citation only
NCT 2014[859]	Citation only
NCT 2014[857]	Citation only
NCT 2015[864]	Citation only
NCT 2015[867]	Citation only
NCT 2016[881]	Citation only
NCT 2016[879]	Citation only
NCT 2017[894]	Citation only
NCT 2017[889]	Citation only
NCT 2017[890]	Citation only
NCT 2017[885]	Citation only
Sinatra 2005[1150]	Inappropriate comparison. Incorrect interventions. IV acetaminophen vs IV propacetamol
Stott 2017[1201]	Cohrane review summary of McNicol 2016
Sun 2018[1213]	Systematic review: references screened
Tzortzopoulou 2011[1282]	Incorrect interventions. Inappropriate comparison. Analysis compared IV paracetamol and IV propacetamol with either placebo or an active comparator, which in turn could be an opioid, NSAID, or other analgesic.
Yang 2017[1388]	Systematic review: references screened

Table 7: Studies excluded from the clinical review of Intravenous paracetamol and intravenous opioid

Study	Exclusion reason
Ali 2009[30]	Inappropriate comparison
Alimian 2014[33]	Inappropriate comparison
Altun 2017[37]	Inappropriate comparison
Api 2009[42]	Inappropriate comparison
Bameshki 2015[71]	Inappropriate comparison
Cattabriga 2007[151]	Inappropriate comparison

Chan 2011[154]	Inappropriate comparison
Divella 2012[246]	Inappropriate comparison
Emir 2010[273]	Nneuro surgery
Gousheh 2013[340]	Inappropriate comparison
Gupta 2016[359]	Inappropriate comparison
Jain 1986[435]	Inappropriate comparison
Jespersen 1989[451]	Non-English language studies
Jespersen 1989[450]	Non-English language studies
Kogan 2007[539]	Inappropriate comparison
Lange 2018[571]	Inappropriate comparison
Levin 1974[603]	Inappropriate comparison
Liashek 1987[612]	Inappropriate comparison
Lin 2012[617]	Inappropriate comparison
Lippmann 1980[620]	citation only
Mackay 1982[651]	Inappropriate comparison
Mitra 2017[727]	Inappropriate comparison
Monrigal 1994[744]	Non-English language studies
Montefiore 1991[746]	Non-English language studies
Moore 1999[748]	Systematic review is not relevant to review question or unclear PICO
NCT 2014[856]	citation only
NCT 2018[901]	citation only
Omar 2011[941]	Inappropriate comparison
Park 2015[981]	Inappropriate comparison
Pereira 2017[995]	Inappropriate comparison
Petti 1985[1000]	Inappropriate comparison
Raffa 2018[1029]	Inappropriate comparison
Rawal 2011[1045]	Inappropriate comparison
Robinson 2015[1063]	Inappropriate comparison
Sawaddiruk 2010[1108]	Inappropriate comparison
Shaffer 2017[1133]	Inappropriate comparison
Singla 2014[1163]	Inappropriate comparison
Singla 2014[1162]	Inappropriate comparison
Skoglund 1984[1167]	Inappropriate comparison
Skoglund 1986[1166]	Inappropriate comparison
Skoglund 1991[1168]	Inappropriate comparison
Smith 2001[1174]	Systematic review is not relevant to review question or unclear PICO
Smith 2004[1172]	Inappropriate comparison
Sunshine 1992[1217]	Incorrect interventions
Sunshine 1996[1216]	Incorrect interventions
Sutters 2011[1219]	Incorrect study design
Tanskanen 1999[1241]	Incorrect interventions
Toms 2009[1262]	Systematic review is not relevant to review question or unclear PICO
Yaghoubi 2013[1381]	Incorrect interventions
Young 1979[1410]	Incorrect interventions

Young 1979[1411]	Incorrect interventions
Zavareh 2013[1424]	Inappropriate comparison
Zeidan 2014[1427]	Inappropriate comparison
Zhang 1996[1436]	Systematic review is not relevant to review question or unclear PICO

H.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 8: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Simple Analgesics: Non-steroidal anti-inflammatory drugs (NSAIDs)

Appendix A: Review protocol

Table 9: Review protocol: Managing acute postoperative pain: NSAIDs

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	What is the most clinically and cost effective strategy for managing acute postoperative pain?
2.	Review question	What is the most clinically and cost effective strategy for managing acute postoperative pain? There are six topic areas that have been identified: Paracetamol routes of delivery Non-steroidal anti-inflammatory drugs (NSAIDs) Opioid administration strategy (Continuous epidural ,intravenous PCA, spinal) Opioid post-operative administration strategy (oral vs iv) Ketamine Neuropathic nerve stabilisers This protocol addresses, 'What is the clinical and cost effectiveness of NSAIDs for managing acute postoperative pain?'
3.	Objective	This is a two-step review to determine in: Step 1 • if NSAIDs are clinically and cost effective for managing acute post-operative pain and then if NSAIDs are demonstrated to be clinically and cost effective compared to placebo Step 2 • Which is the most effective NSAID for managing acute post-operative pain
4.	Searches	The following databases will be searched: • Embase • MEDLINE • The Cochrane Library

		Searches will be restricted by: • English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	What is the most clinically and cost effective strategy for managing acute postoperative pain
6.	Population	Inclusion: Adults (18 years and older) who have undergone surgery. Exclusion: People who have had Surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	Interventions given post operatively: • non-steroidal anti-inflammatory drugs by any route, including : o indomethacin o ibuprofen o diclofenac o naproxen o ketorolac, o COX2- inhibitor (for example, celecoxib)
8.	Comparator/Reference standard/Confounding factors	Comparators: Step 1 • placebo Step 2 • each other[a] [a] A stepped approach will be taken if the evidence shows NSAIDs are clinically and cost effective and within class comparisons will be explored.
9.	Types of study to be included	Randomised controlled trials and systematic reviews of randomised controlled trials
10.	Other exclusion criteria	Non-English language Cross-over randomised controlled trials
11.	Context	NA
12.	Primary outcomes (critical outcomes)	• Health-related quality of life • Pain reduction o < 6 hours post op o 6 hours- 24 hours post op Pain reduction measured by: • patient reported pain (physician, nurse

		or carer reported pain will not be included); • patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both) • patient reported pain intensity expressed hourly over four to six hours using validated pain scales, or reported summed pain intensity difference (SPID) at four to six hours • Number of participants achieving at least 50% pain relief • Time to achieve 50% pain intensity • Amount of additional medication use (rescue medication) o < 6 hours post op o 6 hours- 24 hours post op • Time to rescue medication • Adverse events (including respiratory depression, nausea, vomiting)
13.	Secondary outcomes (important outcomes)	• Psychological distress and mental well-being • Symptom scores • Functional measures • Length of stay in intensive care • Length of stay in hospital • Hospital readmission The committee agreed that a difference of 1 (10%) on a 10 point pain scale such as NRS or VRS indicated a clinically important difference. For the remaining outcomes, the committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.

		Cochrane RoB (2.0) and Risk of Bias in Systematic Reviews (ROBIS) will be used to assess intervention reviews 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management The clinical approach to this area of the scope is multimodal. The pain management approach for each patient will depend on many factors and include the procedure and the severity of pain. For this reason it is not meaningful to compare the drugs listed in the topic areas to each other. There isn't an overall question evaluating which drug is the most effective and a network meta-analysis is not appropriate.	
17.	Analysis of sub-groups	Subgroups: • people aged over 60 years • NSAID potency • Dosage • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation • American Society of Anesthesiologists (ASA) Physical Status grade	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	NA	
22.	Anticipated completion date	NA	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☑
		Piloting of the study selection process	☐ / ☑
		Formal screening of search results against eligibility criteria	☐ / ☑
		Data extraction	☐ / ☑
		Risk of bias (quality) assessment	☐ / ☑
		Data analysis	☐ / ☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swaine Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis	

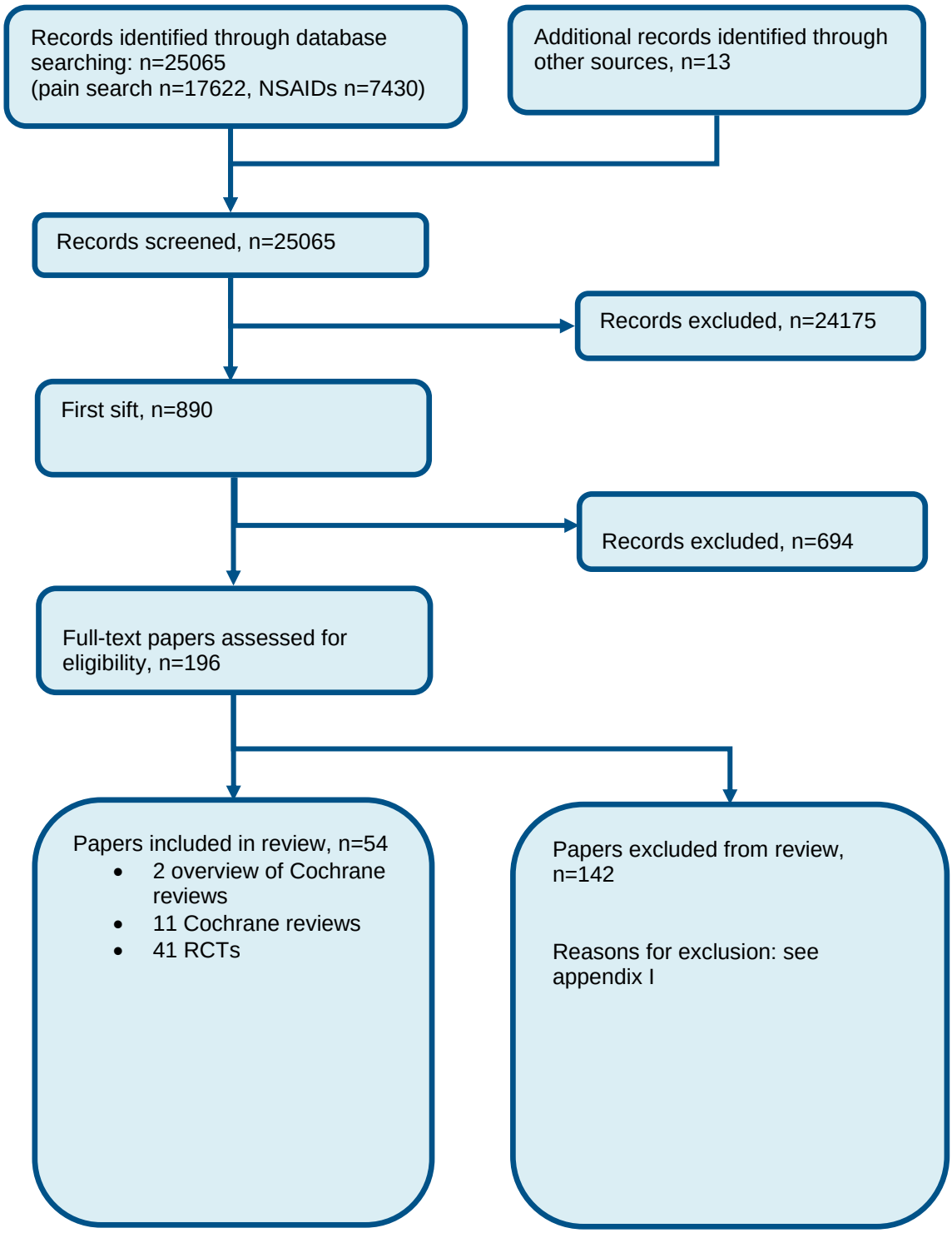
		Ms Lina Gulhane	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details	NA	
30.	Reference/URL for published protocol	NA	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • Issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Perioperative care Pain relief Paracetamol	
33.	Details of existing review of same topic by same authors	NA	
34.	Current review status	☐	Ongoing
		☒	Completed but not published

		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	NA	
36.	Details of final publication	www.nice.org.uk	

The health economic review protocol is shown in Table **3**.

Appendix B: Clinical evidence selection

Figure 25: Flow chart of clinical study selection for the review of NSAIDs



Appendix C: Clinical evidence tables

Study	Moore 2015[749]/Moore 2015[750]
Study type	Overview of Cochrane reviews
Number of studies (number of participants)	(39 Cochrane reviews, 460 individual studies, ~ 50,000 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. All Cochrane reviews of randomised controlled trials (RCTs) of single dose oral analgesics for acute postoperative pain in adults (aged 15 years or greater).
Stratum	Overall
Selection of studies	Included reviews assessed RCTs evaluating the effects of a single oral dose of analgesic given f or relief of moderate to severe postoperative pain in adults, compare d with placebo, and included: a clearly defined clinical question details of inclusion and exclusion criteria details of databases searched and relevant search strategies participant-reported pain relief summary results for at least one desired outcome
Exclusion criteria	Not reported
Indirectness of population	No indirectness
Interventions	Single dose oral analgesics for acute postoperative pain
Outcomes reported	At least 50% maximum pain relief over 4 - 6 hours Participants with at least one adverse event
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Derry 2012[236]
Study type	Cochrane review
Number of studies (number of participants)	67 studies (5743 participants)
Line of therapy	Adjunctive to current care. Single dose intervention

Study	Derry 2012[236]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral aspirin compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	review articles, case reports, and clinical observations; studies of experimental pain; studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Aspirin or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: patient reported pain at baseline patient reported pain relief patient global assessment of efficacy (PGE) time to use of rescue medication number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Gaskell 2017[321]
Study type	Cochrane review
Number of studies (number of participants)	24 studies (5220 participants)
Line of therapy	Adjunctive to current care. Single dose intervention

Study	Gaskell 2017[321]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral dexketoprofen or ketoprofen compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	review articles, case reports, and clinical observations; studies of experimental pain; studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Dexketoprofen, Ketoprofen or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Primary outcomes: Participants achieving at least 50% pain relief over four to six hours after taking the medication. Secondary outcomes Median (or mean) time to use of rescue medication. Number of participants using rescue medication over four to six hours after taking the medication. 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. 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.
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Derry 2015[238]
Study type	Cochrane review
Number of studies (number of participants)	18 studies (3714 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with

Study	Derry 2015[238]
condition	established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral diclofenac compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	review articles, case reports, and clinical observations; studies of experimental pain; studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Diclofenac or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: patient reported pain at baseline patient reported pain relief patient global assessment of efficacy (PGE) time to use of rescue medication number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Wasey 2010[1338]
Study type	Cochrane review
Number of studies (number of participants)	9 studies (906 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with

Study	Wasey 2010[1338]
condition	established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral diflunisal compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	review articles, case reports, and clinical observations; studies of experimental pain; studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Diflunisal or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: patient reported pain at baseline patient reported pain relief patient global assessment of efficacy (PGE) time to use of rescue medication number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Tirunagari 2009[1258]
Study type	Cochrane review
Number of studies (number of participants)	9 studies (1459 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with

Study	Tirunagari 2009[1258]
condition	established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral etodolac compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	review articles, case reports, and clinical observations; reports of trials concerned with pain other than postoperative pain (including experimental pain); studies using healthy volunteers; studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Etodolac or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: pain model; patient-reported pain at baseline patient-reported pain relief and/or pain intensity expressed hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours; patient global assessment of efficacy (PGE) time to use of rescue medication number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Sultan 2009[1210]
Study type	Cochrane review

Study	Sultan 2009[1210]
Number of studies (number of participants)	11 studies (1061 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral flurbiprofen compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	posters or abstracts not followed up by full publication; reports of trials concerned with pain other than postoperative pain (including experimental pain); studies using healthy volunteers; studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Flurbiprofen or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: pain model; patient-reported pain at baseline patient-reported pain relief and/or pain intensity expressed hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours; patient global assessment of efficacy (PGE) time to use of rescue medication number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	**Sultan 2009[1210]**
Study	Derry 2009[235]
Study type	Cochrane review
Number of studies (number of participants)	72 studies (9186 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral ibuprofen compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	• posters or abstracts not followed up by full publication; • reports of trials concerned with pain other than postoperative pain (including experimental pain); • studies using healthy volunteers; • studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); • studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Ibuprofen or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: • pain model; • patient-reported pain at baseline • patient-reported pain relief and/or pain intensity expressed hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours; • patient global assessment of efficacy (PGE) • time to use of rescue medication • number of participants using rescue medication • number of participants with one or more adverse events • number of participants with serious adverse events • number of withdrawals (all-cause, adverse events)

Study	Sultan 2009[1210]
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Derry 2009[235]
Study type	Cochrane review
Number of studies (number of participants)	72 studies (9186 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral ibuprofen compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	posters or abstracts not followed up by full publication; reports of trials concerned with pain other than postoperative pain (including experimental pain); studies using healthy volunteers; studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Ibuprofen or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: pain model; patient-reported pain at baseline patient-reported pain relief and/or pain intensity expressed hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours; patient global assessment of efficacy (PGE) time to use of rescue medication

Study	Derry 2009[235]
	number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Moll 2011[740]
Study type	Cochrane review
Number of studies (number of participants)	4 studies (842 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral mefenamic acid compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	posters or abstracts not followed up by full publication; reports of trials concerned with pain other than postoperative pain (including experimental pain); studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Mefenamic acid or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: patient reported pain at baseline patient reported pain relief patient global assessment of efficacy (PGE) time to use of rescue medication

Study	Moll 2011[740]
	number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Derry 2013[237]
Study type	Cochrane review
Number of studies (number of participants)	10 studies (1785 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral celecoxib compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	posters or abstracts not followed up by full publication; reports of trials concerned with pain other than postoperative pain (including experimental pain); studies using healthy volunteers; studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Celecoxib acid or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: pain model; patient-reported pain at baseline patient-reported pain relief and/or pain intensity expressed hourly over four to six hours using validated pain

Study	Derry 2013[237]
	scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours; patient global assessment of efficacy (PGE) time to use of rescue medication number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Clarke 2012[190]
Study type	Cochrane review
Number of studies (number of participants)	6 studies (1214 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral etoricoxib compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	posters or abstracts not followed up by full publication; reports of trials concerned with pain other than postoperative pain (including experimental pain); studies using healthy volunteers; studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); studies of less than four h ours duration or studies that fail to present data over four to six hours post-dose.
Indirectness of population	No indirectness
Interventions	Etoricoxib acid or matched placebo administered as a single oral dose for postoperative pain.

Study	Clarke 2012[190]
Outcomes reported	Data collected included: pain model; patient-reported pain at baseline patient-reported pain relief and/or pain intensity expressed hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours; patient global assessment of efficacy (PGE) time to use of rescue medication number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Roy 2010[1075]
Study type	Cochrane review
Number of studies (number of participants)	4 studies (629 participants)
Line of therapy	Adjunctive to current care. Single dose intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis. Included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.
Stratum	Overall
Selection of studies	Double-blind trials of single dose oral lumiracoxib compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Included multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately.
Exclusion criteria	Abstracts, review articles, case reports, and clinical observations were excluded, as were reports that did not clearly state that the interventions had been randomly allocated, were concerned with other pain conditions, or used experimental pain or volunteer participants, or both.
Indirectness of population	No indirectness

Study	Roy 2010[1075]
Interventions	Lumiracoxib acid or matched placebo administered as a single oral dose for postoperative pain.
Outcomes reported	Data collected included: pain model; patient-reported pain at baseline patient-reported pain relief and/or pain intensity expressed hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours; patient global assessment of efficacy (PGE) time to use of rescue medication number of participants using rescue medication number of participants with one or more adverse events number of participants with serious adverse events number of withdrawals (all-cause, adverse events)
Risk of bias assessment	Overall risk of bias – low risk of bias, Study eligibility criteria – low concern, Identification and selection of studies – low concern, Data collection and study appraisal – low concern, Synthesis and findings – low concern

Study	Aftab 2008[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Pakistan; Setting: department of Anesthesiology and Surgical Intensive Care Unit, Civil Hospital Karachi.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA physical status I and II, age ranged 45 – 50 years
Exclusion criteria	Patients with history of allergic reaction to non-steroidal anti-inflammatory drugs, bronchial asthma,

Study	Aftab 2008[12]
	gastrointestinal ulceration, bleeding disorder and patients with cardiac, renal, hepatic dysfunction were excluded from study.
Recruitment/selection of patients	undergoing elective laparoscopy surgery
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 44.17 ± 12.05; Diclofenac: 43.50 ± 12.56. Gender (M:F): 11/49. Ethnicity:
Further population details	1. Age: <60 years (Ketorolac: 44.17 ± 12.05; Diclofenac: 43.50 ± 12.56). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 51; ASA II: 9). 3. Type of surgery: lower and upper GI (laparoscopy surgery). 4. Ketorolac 30mg; Diclofenac 75mg
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. During the postoperative period received Ketorolac 30mg IV 8 hourly. Duration Unclear - not specified . Concurrent medication/care: Rescue analgesic medication consisting of nalbuphine 0.1mg/kg was administered to patients if pain persistently remained above two on visual analogue scale.. Indirectness: No indirectness (n=30) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. During the postoperative period received Diclofenac 75mg IV 12 hourly. Duration Unclear - not specified. Concurrent medication/care: Rescue analgesic medication consisting of nalbuphine 0.1mg/kg was administered to patients if pain persistently remained above two on visual analogue scale.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Nalbuphine consumption at 0-4 hours; Group 1: mean 1.3 milligrams (SD 3.01); n=30, Group 2: mean 2.57 milligrams (SD 3.11); n=30; Comments: p value 0
Risk of bias: All domain - High, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Nalbuphine consumption at 20-24 hours; Group 1: mean 0 milligrams (SD 0); n=30, Group 2: mean 0 milligrams (SD 0); n=30; Comments: P value not significant
Risk of bias: All domain - High, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal

Study	Aftab 2008[12]
complications, bone healing complications) - Actual outcome: Nausea & Vomiting at postoperative; Group 1: 5/30, Group 2: 2/30; Comments: Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Akinbade 2018[21]
Study type	Systematic Review
Number of studies (number of participants)	(n=135)
Countries and setting	Conducted in Nigeria; Setting: University Teaching Hospital, Nigeria
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with at least one impacted mandibular third molar that was indicated for surgical extraction and confirmed by radiographs with the absence of uncontrolled medical or systemic conditions.
Exclusion criteria	Acute infection involving the mandibular third molar in question, unerupted mandibular third molar that is deeply buried in bone, uncontrolled medical or systemic disease, history of allergy or hypersensitivity to Ibuprofen, Celecoxib, Tramadol, Amoxycillin and Metronidazole, peptic ulcer disease, pregnancy or lactation, and a history of psychological or physical dependence on opioids as well as history of analgesic use in 24 hours before the extraction.
Recruitment/selection of patients	Patients with at least one impacted mandibular third molar that was indicated for surgical extraction
Age, gender and ethnicity	Age - Mean (SD): Ibuprofen: 27.22 (7.13); Celecoxib: 26.56 (6.29). Gender (M:F): 33/57. Ethnicity: NA:
Further population details	1. Age: <60 years (Ibuprofen: 27.22 (7.13); Celecoxib: 26.56 (6.29)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable

Study	Akinbade 2018[21]
	(Dental surgery). 4. Ibuprofen 400mg; Celecoxib 400mg.
Indirectness of population	--
Interventions	(n=45) Intervention 1: Non-steroidal anti-inflammatory - Ibuprofen. Ibuprofen 400mg every 8 hours as needed for 48 hours .. Duration Postoperative 48 hours. Concurrent medication/care: Amoxicillin 500mg 8 hourly and metronidazole 400mg 8 hourly for 5 days. Indirectness: No indirectness (n=45) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Celecoxib 400mg to start and then 200mg every 12 hours for 48 hours as needed.. Duration postoperative 48 hours. Concurrent medication/care: Amoxicillin 500mg 8 hourly and metronidazole 400mg 8 hourly for 5 days. Indirectness: No indirectness
Funding	Funding not stated
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Al-Sukhun 2011[24]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=458)
Countries and setting	Conducted in Finland; Setting: Oral institute/hospital, Finland
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I scheduled to undergo surgical removal of a mandibular molar

Study	Al-Sukhun 2011[24]
Exclusion criteria	Any conditions that contraindicated the use of NSAIDs or COX-2 inhibitors, were pregnant or nursing, were taking psychotropic medications, or had active ulcers or gastrointestinal bleeding, liver dysfunction or kidney dysfunction.
Recruitment/selection of patients	scheduled to undergo surgical removal of a mandibular molar
Age, gender and ethnicity	Age - Mean (SD): Mean age: 38.9 (7.7). Gender (M:F): 152/157. Ethnicity: NA:
Further population details	1. Age: <60 years (Mean age: 38.9 (7.7)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 3. Type of surgery: Not applicable (Dental surgery). 4. Ibuprofen 400mg; Celecoxib 200mg.
Indirectness of population	No indirectness
Interventions	(n=162) Intervention 1: Non-steroidal anti-inflammatory - Ibuprofen. 400mg Ibuprofen 1 hour before surgery. Duration single administration. Concurrent medication/care: 1g of paracetamol as rescue medication if needed. Indirectness: No indirectness (n=147) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. 200mg Celecoxib 1 hour before surgery. Duration single administration. Concurrent medication/care: 1g of paracetamol as rescue medication if needed. Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus CELECOXIB Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea at postoperatively; Group 1: 27/162, Group 2: 22/147 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Headache at postoperatively; Group 1: 15/162, Group 2: 17/147 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Al-Sukhun 2011[24]**
Study	Al-Sukhun 2012[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=150)
Countries and setting	Conducted in Finland; Setting: Oral and maxillofacial surgery centre, Finland
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients ASA I, aged 18 - 72, scheduled to undergo surgical removal of an impacted mandibular third molar.
Exclusion criteria	Any medical conditions that contraindicated the use of NSAIDs and COX-2 inhibitors, were pregnant or nursing, had psychological or psychiatric conditions, were taking psychotropic medications or had active ulcers or GI bleeding, liver dysfunction, inflammatory intestinal disease or decreased kidney function.
Recruitment/selection of patients	scheduled to undergo surgical removal of an impacted mandibular third molar
Age, gender and ethnicity	Age - Mean (SD): Ibuprofen: 29.1 (7.9); Celecoxib: 30.3 (5.5). Gender (M:F): 47/46. Ethnicity: NA:
Further population details	1. Age: <60 years (Ibuprofen: 29.1 (7.9); Celecoxib: 30.3 (5.5)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 3. Type of surgery: Not applicable (Dental surgery). 4. Ibuprofen 200mg; Celecoxib 200mg.
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Non-steroidal anti-inflammatory - Ibuprofen. 200mg Ibuprofen 1 hour before surgery. Duration single administration. Concurrent medication/care: 1g paracetamol as rescue medication if needed. Indirectness: No indirectness (n=48) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. 200mg Celecoxib 1 hour before surgery. Duration single administration. Concurrent medication/care: 1g of paracetamol as rescue medication if needed. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus CELECOXIB

Study	Al-Sukhun 2011[24]
Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: TOPAR (total pain relief) at 12 hours postoperatively; Ibuprofen: 16.9 (14.0-19.3) Celecoxib: 27.1 (24.0-29.7) 0-48 Top=High is good outcome, Comments: p value < 0.001; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Argoff 2016[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=428)
Countries and setting	Conducted in USA; Setting: Tertiary medical hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	aged 18 to 65 years old with a body mass index) <40kg/m2 and a body weight □45kg, and who experienced moderate-to-severe pain (>40mm/100mm by VAS) following bunionectomy surgery
Exclusion criteria	Participants in previous SoluMatrix diclofenac clinical trials or in any studies of investigational drugs or devices within 30 days prior to the present study were excluded. Other exclusions included: clinically significant intolerance or allergy to any study drug; a history of alcoholism or drug abuse within 2 years prior to enrollment; a clinically significant GI event within 6 months prior to enrollent such as a history of peptic or gastric ulcers, GI bleeding, or perforation; and surgical or medical conditions of the GI or renal systems that might alter the absorption, distribution, or excretion of drug substances.
Recruitment/selection of patients	Scheduled for bunionectomy surgery
Age, gender and ethnicity	Age - Mean (SD): 39.7 ± 12.0 years. Gender (M:F): 57/371. Ethnicity: NA:
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (Bunionectomy surgery). 4. Diclofenac 18 – 35mg; Celecoxib 200 – 400mg.
Indirectness of population	No indirectness
Interventions	(n=216) Intervention 1: Non-steroidal anti-inflammatory - Diclofenac. Patients who reported pain intensities ≥40mm were randomized to receive either low-dose SoluMatrix diclofenac 18mg or 35mg capsules three times daily. Duration 48 hours postoperatively. Concurrent medication/care: Patients were permitted to receive opioid-containing rescue medication (hydrocodone/acetaminophen tablet 10mg/325mg every 4–6h or oxycodone/acetaminophen tablet 7.5mg/325mg every 6h) up to six tablets per day as needed prior to randomization for breakthrough pain or as rescue medication throughout the study. Indirectness: No indirectness

	(n=106) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Patients who reported pain intensities ≥40mm were randomized to receive celecoxib 400mg loading dose followed by 200-mg capsules twice daily. Duration 48 hours. Concurrent medication/care: Patients were permitted to receive opioid-containing rescue medication (hydrocodone/acetaminophen tablet 10mg/325mg every 4–6h or oxycodone/acetaminophen tablet 7.5mg/325mg every 6h) up to six tablets per day as needed prior to randomization for breakthrough pain or as rescue medication throughout the study. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Iroko Pharmaceuticals, LLC, Philadelphia, PA.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus CELECOXIB Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea at postoperative; Group 1: 59/216, Group 2: 29/106 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: discontinuation by investigator; Group 2 Number missing: 1, Reason: discontinuation due to lack of efficacy - Actual outcome: Vomiting at postoperative; Group 1: 20/216, Group 2: 15/106 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: discontinuation by investigator; Group 2 Number missing: 1, Reason: discontinuation due to lack of efficacy - Actual outcome: Dizziness at postoperative; Group 1: 22/216, Group 2: 11/106 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: discontinuation by investigator; Group 2 Number missing: 1, Reason: discontinuation due to lack of efficacy - Actual outcome: Headache at postoperative; Group 1: 28/216, Group 2: 11/106 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: discontinuation by investigator; Group 2 Number missing: 1, Reason: discontinuation due to lack of efficacy - Actual outcome: Pruritis at postoperative; Group 1: 10/216, Group 2: 4/106 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: discontinuation by investigator; Group 2 Number missing: 1, Reason: discontinuation due to lack of efficacy	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological

	distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Bakshi 1994[68]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=245)
Countries and setting	Conducted in Germany; Setting: Centre for oral and maxillofacial diseases, Germany
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Up to the age of 65, suffering from at least severe pain after surgical extraction of an impacted lower third molar
Exclusion criteria	Hypersensitivity to diclofenac or Ibuprofen, history of GI bleeding or peptic ulceration; presence of severe hepatic, renal, cardiac or hemopoietic disorder and pregnancy/lactation.
Recruitment/selection of patients	suffering from at least severe pain after surgical extraction of an impacted lower third molar
Age, gender and ethnicity	Age - Mean (range): Diclofenac: 27.7 (18-68); Ibuprofen: 26.9 (18-60). Gender (M:F): 108/55. Ethnicity: NA
Further population details	1. Age: <60 years (Diclofenac: 27.7 (18-68); Ibuprofen: 26.9 (18-60)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable 3. Type of surgery: Not applicable (Dental surgery). 4. Diclofenac 50mg; Ibuprofen 400mg.
Indirectness of population	No indirectness
Interventions	(n=83) Intervention 1: Non-steroidal anti-inflammatory - Diclofenac. Diclofenac dispersible 50mg . Duration unclear. Concurrent medication/care: rescue analgesia unclear. Indirectness: Serious indirectness; Indirectness comment: rescue analgesia not specified (n=80) Intervention 2: Non-steroidal anti-inflammatory - Ibuprofen. Ibuprofen 400mg postoperatively . Duration unclear. Concurrent medication/care: rescue analgesia unclear. Indirectness: Serious indirectness; Indirectness comment: rescue analgesia not specified

Funding	Principal author funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus IBUPROFEN Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain score at 6 hours postoperatively; Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Barton 2002[80]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=202)
Countries and setting	Conducted in USA; Setting: LDS Hospital, Salt Lake City, Utah
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	women aged 18–64 yr requiring parenteral analgesia for moderate or severe pain after elective total abdominal hysterectomy or myomectomy, but who were otherwise generally healthy
Exclusion criteria	Patients were excluded if they were scheduled to undergo surgery likely to produce greater surgical trauma than the hysterectomy or myomectomy alone; had GI bleeding or esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days before receipt of study medication; were experiencing significant GI complaints; had received any analgesic (including neuroleptic), antipsychotic, or corticosteroid drugs, other than those required for surgery, within 6 h before surgery (or

	longer if long-acting or sustained-release formulations of the medication were used); or were hypersensitive to any NSAID, COX-2–specific inhibitors, opiates, or any analgesic agent with cross-reactivity to the study drugs. If a patient had been diagnosed with, treated for, or was in remission from any cancer other than basal cell carcinoma or metastatic uterine carcinoma within 2 yr before screening, they were also excluded.
Recruitment/selection of patients	elective total abdominal hysterectomy or myomectomy
Age, gender and ethnicity	Age - Mean (range): Ketorolac: 40.8 (27-52); Parecoxib: 42.8 (21-65). Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 40.8 (27-52); Parecoxib: 42.8 (21-65)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (abdominal hysterectomy or myomectomy). 4. Ketorolac 30mg; Parecoxib 20 – 40mg.
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. Patients who developed a level of pain that measured at least 45 mm on a visual analog scale (VAS; ranging, 0–100 mm) and a categorical pain intensity of moderate or severe within 6 h after discontinuation of patient-controlled analgesia were then randomized to receive one intravenous dose of ketorolac, 30 mg. Duration POD 1. Concurrent medication/care: After surgery, patient-controlled analgesia was provided with morphine sulfate, 0.5–2 mg/dose, or meperidine hydrochloride, 10–30 mg/dose, with a 10-min lockout between doses. Basal infusions of morphine, 0.5–1.0 mg/h, or meperidine hydrochloride, 10–30 mg/h, were permitted in addition to the patient-controlled doses.. Indirectness: No indirectness (n=77) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Patients who developed a level of pain that measured at least 45 mm on a visual analog scale (VAS; ranging, 0–100 mm) and a categorical pain intensity of moderate or severe within 6 h after discontinuation of patient-controlled analgesia were then randomized to receive one intravenous dose of Parecoxib (20 or 40mg). Duration POD 1. Concurrent medication/care: After surgery, patient-controlled analgesia was provided with morphine sulfate, 0.5–2 mg/dose, or meperidine hydrochloride, 10–30 mg/dose, with a 10-min lockout between doses. Basal infusions of morphine, 0.5–1.0 mg/h, or meperidine hydrochloride, 10–30 mg/h, were permitted in addition to the patient-controlled doses.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)

- Actual outcome: Nausea at Postoperative; Group 1: 17/41, Group 2: 25/77 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at Postoperative; Group 1: 11/41, Group 2: 15/77 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Abdominal pain at Postoperative; Group 1: 12/41, Group 2: 18/77 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Bikhazi 2004[107]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=208)
Countries and setting	Conducted in USA; Setting: Tertiary medical centre
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were 18-64 with a body weight of at least 50kg. THey had undergone elective total abdominal hysterectomy (with or without salpingo-oopherectomy or minor bladder repair) or myomectomy through a low transverse or low midline incision under general anesthesia.
Exclusion criteria	During the 6 hours preceding surgery, if patients had received agents that could confound analgesic response specifically, analgesics, neuroleptics, anytipsychotic agents and corticosteroids they were excluded. Hypersensitivity or cross-sensitivity to study medications was also an exclusion criteria.
Recruitment/selection of patients	They had undergone elective total abdominal hysterectomy (with or without salpingo-oopherectomy or minor

	bladder repair) or myomectomy
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 44.7 (8.2); Parecoxib: 41.56 (7.58). Gender (M:F): all female . Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 44.7 (8.2); Parecoxib: 41.56 (7.58)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (Surgical hysterectomy). 4. Ketorolac 30mg; Parecoxib 20 – 40mg.
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. Within 6 hours of discontinuing PCA, patients were given 30mg Ketorolac IV. Study medication was readministered as required at 6 hour intervals up to a maximum of 120mg Ketorolac per 24 hours. Patients had to have moderate or severe pain score on a visual analogue scale >45mm. Duration up to 5 days postoperatively. Concurrent medication/care: Only non study medications were given (as rescue medications) before the second administration of study medications. If rescue was needed after the second administration, then the patients were withdrawn. . Indirectness: No indirectness (n=81) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Within 6 hours of discontinuing PCA, patients were given 20 OR 40mg Parecoxib IV. Study medication was readministered as required at 6 hour intervals up to a maximum of 80mg Parecoxib per 24 hours. Patients had to have moderate or severe pain score on a visual analogue scale >45mm. Duration up to 5 days postoperatively. Concurrent medication/care: Only non study medications were given (as rescue medications) before the second administration of study medications. If rescue was needed after the second administration, then the patients were withdrawn. . Indirectness: No indirectness
Funding	Study funded by industry (study funded by Pfizer global pharmaceuticals and pharmacia corporation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Headache at postoperatively; Group 1: 3/27, Group 2: 5/39
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: withdrawal or protocol violation; Group 2 Number missing: 42, Reason: withdrawal or protocol violation
- Actual outcome: Abdominal pain at postoperatively; Group 1: 0/27, Group 2: 7/39
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: withdrawal or protocol violation; Group 2 Number missing: 42, Reason: withdrawal or protocol violation

- Actual outcome: vomiting at postoperatively; Group 1: 1/27, Group 2: 2/39 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15, Reason: withdrawal or protocol violation; Group 2 Number missing: 42, Reason: withdrawal or protocol violation	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Canadell-Carafi 1990[143]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=76)
Countries and setting	Conducted in Spain; Setting: University Hospital, Spain
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 - 65 suffering moderate to severe pain following orthopaedic surgery (total hip replacement, lumbar arthrodesis)
Exclusion criteria	significant impairment of the brain, liver, kidney, lung or heart function; those with altered endocrine function; gastric or duodenal ulcer; asthma; allergy to salicylates or non steroidals,; hypersensitivity to diclofenac; addiction to alcohol or other drugs; and pregnant or breast feeding were excluded from this study.
Recruitment/selection of patients	participants who underwent orthopedic surgery
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 41.9 (15.9); Diclofenac: 37.8 (16.8). Gender (M:F): 46/30. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 41.9 (15.9); Diclofenac: 37.8 (16.8)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (total hip replacement, lumbar arthrodesis). 4. Ketorolac 10mg; Diclofenac 100mg.
Indirectness of population	No indirectness

Interventions	(n=37) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. 10mg Ketorolac suppositories, four times a day. Duration unspecified . Concurrent medication/care: rescue medication as paracetamol 500mg two hours after administration of study medications (n=39) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. Diclofenac 100mg suppositories, given twice a day. Duration unspecified. Concurrent medication/care: rescue medication as paracetamol 500mg two hours after administration of study medications. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: TOTPAR 6 hours at 6 hours postoperatively; Group 1: mean 421.1 (SD 122.2); n=37, Group 2: mean 411.7 (SD 138.8); n=39; Comments: p value 0.755421.1 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Cheung 2007[169]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=171)
Countries and setting	Conducted in USA; Setting: Two dental centres, Utah, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	>18 years and in good health, who had undergone surgical extraction of at least 2 impacted third molar teeth (1 of which was a fully or partially impacted mandibular requiring bone removal), had a baseline pain intensity score of ≥50 mm on a 100-ram visual analog scale (VAS), and were experiencing moderate or severe postsurgical pain.
Exclusion criteria	Patients were excluded from the study if they had started treatment for GI ulceration within 30 days prior to surgery, used analgesics or other agents during the 24 hours preceding surgery, or had a history of known analgesic or narcotic abuse. In addition, patients were ineligible for study participation if they were pregnant or breastfeeding; unwilling to abstain from the use of alcohol for the study duration; had a known hypersensitivity to analgesics, conventional NSAIDs, COX inhibitors, or sulfonamides
Recruitment/selection of patients	who had undergone surgical extraction of at least 2 impacted third molar teeth
Age, gender and ethnicity	Age - Mean (SD): Ibuprofen: 22.0 (4.7); Celecoxib: 21.4 (4.2). Gender (M:F): 54/60. Ethnicity: NA
Further population details	1. Age: <60 years (Ibuprofen: 22.0 (4.7); Celecoxib: 21.4 (4.2)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not stated / Unclear (Dental surgery). 4. Ibuprofen 400mg; Celecoxib 400mg.
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Non-steroidal anti-inflammatory - Ibuprofen. Patients received a single, oral dose of ibuprofen 400 mg on experiencing moderate or severe pain with a baseline pain intensity score >50 mm on a 0-100-mm VAS within 6 hours of third molar extraction.. Duration 24 hours postoperatively. Concurrent medication/care: Rescue medication given but not stated.. Indirectness: No indirectness (n=57) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Patients received a single, oral dose of Celecoxib 400 mg on experiencing moderate or severe pain with a baseline pain intensity score >50 mm on a 0-100-mm VAS within 6 hours of third molar extraction.. Duration 24 hours postoperatively. Concurrent medication/care: Rescue medication given but not stated.. Indirectness: No indirectness
Funding	Study funded by industry (funded by Pfizer Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus CELECOXIB

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: TOTPAR score at 6 hours postoperively; Group 1: mean 14.9 (SD 6.2); n=30, Group 2: mean 13.4 (SD 5.9); n=16
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 27, Reason: lack of efficacy and adverse events; Group 2 Number

missing: 41, Reason: lack of efficacy - Actual outcome: TOTPAR score at 24 hours postoperively; Group 1: mean 38.3 (SD 27.8); n=30, Group 2: mean 48.8 (SD 29.6); n=16 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: lack of efficacy and adverse events; Group 2 Number missing: 41, Reason: lack of efficacy Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea at Postoperively; Group 1: 16/30, Group 2: 9/16 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: lack of efficacy and adverse events; Group 2 Number missing: 41, Reason: lack of efficacy - Actual outcome: Vomiting at Postoperively; Group 1: 7/30, Group 2: 3/16 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: lack of efficacy and adverse events; Group 2 Number missing: 41, Reason: lack of efficacy - Actual outcome: Headache at Postoperively; Group 1: 11/30, Group 2: 9/16 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: lack of efficacy and adverse events; Group 2 Number missing: 41, Reason: lack of efficacy	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Christensen 2011[183]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=353)
Countries and setting	Conducted in USA; Setting: Tufts University School of Medicine, Boston, Massachusetts
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	subjects between 18 and 75 years of age who were undergoing surgical extraction of 1 or more third molars (1 of which was a fully or partially impacted mandibular third molar requiring bone removal) were eligible for enrollment. Subjects had to be in good health as determined by the investigator on the basis of medical history and physical examination and had to have moderate or severe pain within 6 hours after completion of surgery, as measured by a categorical pain intensity scale (moderate or severe descriptor) and pain intensity of ≥50 mm on a 100mmvisualanalog scale (VAS)at baseline.
Exclusion criteria	Female subjects of childbearing potential were required to have a negative pregnancy test and had to be practicing abstinence or a medically acceptable form of contraception plus using a spermicidal agent.
Recruitment/selection of patients	Male and female subjects between 18 and 75 years of age who were undergoing surgical extraction of 1 or more third molars
Age, gender and ethnicity	Age - Mean (SD): 23.7 years . Gender (M:F): 315/218. Ethnicity: NA
Further population details	1. Age: <60 years (23.7). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (Dental). 4. Ketorolac 30mg; Diclofenac 3.75mg – 75mg.
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. ketorolac tromethamine 30 mg was administered as an intravenous (IV) bolus injection over 15 seconds into a pre-placed cannula in the arm. . Duration Intraoperative. Concurrent medication/care: The most common rescue medications taken were oral ibuprofen 400^600 mg and a combination oral analgesic containing hydrocodone 5 mg and acetaminophen 500 mg.. Indirectness: No indirectness (n=255) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. IV diclofenac doses (3.75mg, 9.4mg, 18.75mg, 37.5 mg, or 75mg) was administered as an intravenous (IV) bolus injection over 15 seconds into a pre-placed cannula in the arm.. Duration intraoperative. Concurrent medication/care: The most common rescue medications taken were oral ibuprofen 400^600 mg and a combination oral analgesic containing hydrocodone 5 mg and acetaminophen 500 mg.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (The studywas sponsored byJavelin Pharmaceuticals Inc, which was subsequently acquired by Hospira Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC	

Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Total Pain Relief (TOTPAR6) at First 6 Hours Post Dose; Group 1: mean 400.3 (SD 170.58); n=47, Group 2: mean 270.1 (SD 187.2); n=255 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Chui 1995[185]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Hong Kong (China); Setting: Prince of Wales Hospital, Hong Kong
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II scheduled for elective laparoscopic sterilization
Exclusion criteria	history of psychiatric illness, peptic ulceration, bleeding disorders, renal impairment, or hypersensitivity to NSAIDs.
Recruitment/selection of patients	scheduled for elective laparoscopic sterilization
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 33.5 (3.3); Diclofenac: 33.4 (4.4). Gender (M:F): all female . Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 33.5 (3.3); Diclofenac: 33.4 (4.4)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: gynae-oncology (laparoscopic sterilization). 4. Ketorolac 30mg; Diclofenac 75mg.
Indirectness of population	No indirectness

Interventions	(n=25) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. Ketorolac 30mg IM 30 - 90 minutes before surgery. Duration single administration. Concurrent medication/care: Parenteral pethidine given if analgesia not adequate. . Indirectness: No indirectness (n=25) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. Diclofenac 75mg IM 30 - 90 minutes before surgery. Duration single administration. Concurrent medication/care: parenteral pethidine given if analgesia inadequate. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea and vomiting at postoperatively; Group 1: 11/25, Group 2: 11/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Other side effects at postoperatively; Group 1: 4/25, Group 2: 14/25; Comments: other side effects include back pain, dyspepsia or injection site pain Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Daniels 2001[219]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=304)
Countries and setting	Conducted in USA; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention + follow up:

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18-64; undergoing extraction of ≥ 2 impacted third molars (≥1 of which was mandibular) requiring bone removal. Before enrollment patients had to be experiencing moderate to severe pain on visual analogue scale within 6 hours of surgery.
Exclusion criteria	History of upper GI ulceration or bleeding within 6 months or current significant upper GI complaints. Pregnant women and patients who had taken analgesics or other agents that could confound the analgesic response in the 6 hours before surgery were also excluded.
Recruitment/selection of patients	undergoing extraction of ≥ 2 impacted third molars (≥1 of which was mandibular) requiring bone removal
Age, gender and ethnicity	Age - Other: (Mean age) Ketorolac: 22.5; Parecoxib: 21.4. Gender (M:F): Define. Ethnicity: NA
Further population details	1. Age: <60 years ((Mean age) Ketorolac: 22.5; Parecoxib: 21.4). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable 3. Type of surgery: Not applicable (Dental surgery). 4. Ketorolac 60mg; Parecoxib 20 – 40mg.
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. Ketorolac 60mg IM, after developing moderate to severe postoperative pain after oral surgery. Duration single administration. Concurrent medication/care: rescue medication was given at the discretion of the investigator according to their current practice (medications not specified) (n=101) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Parecoxib 20mg or 40mg IM, after developing moderate to severe postoperative pain after oral surgery. Duration single administration. Concurrent medication/care: rescue medication was given at the discretion of the investigator according to their current practice (medications not specified). Indirectness: No indirectness
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Nausea at postoperatively; Group 1: 5/51, Group 2: 10/101
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

- Actual outcome: Vomiting at postoperatively; Group 1: 3/51, Group 2: 3/101 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Headache at postoperatively; Group 1: 7/51, Group 2: 7/101 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0 - Actual outcome: Pruritis at postoperatively; Group 1: 1/51, Group 2: 0/101 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Doyle 2002[252]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=174)
Countries and setting	Conducted in USA; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients scheduled to undergo surgical removal of one or more impacted third molars were eligible for inclusion. Patients must have experienced at least moderate pain.
Exclusion criteria	serious medical condution; were pregnant; had a history of bleeding disorders, peptic ulcer disease, alcoholism, or substance abuse; depression.
Recruitment/selection of patients	scheduled to undergo surgical removal of one or more impacted third molars were eligible for inclusion. Patients must have experienced at least moderate pain.
Age, gender and ethnicity	Age - Mean (SD): Ibuprofen: 21.8 (6.0); Celecoxib: 21.1 (4.8). Gender (M:F): 63/85. Ethnicity: NA
Further population details	1. Age: <60 years (Ibuprofen: 21.8 (6.0); Celecoxib: 21.1 (4.8)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable 3. Type of surgery: Not applicable (Dental surgery). 4. Ibuprofen 400mg; Celecoxib 200mg.
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Non-steroidal anti-inflammatory - Ibuprofen. Ibuprofen liquigel capsules 400mg . Duration three doses only. Concurrent medication/care: rescue analgesia given but not specified. Indirectness: Serious indirectness; Indirectness comment: rescue analgesia given but not specified (n=74) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Celecoxib 200mg . Duration one dose only. Concurrent medication/care: rescue analgesia given but not specified. Indirectness: Serious indirectness; Indirectness comment: rescue analgesia given but not specified
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus CELECOXIB	

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea at postoperatively; Group 1: 1/74, Group 2: 3/74; Comments: 0.572 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 1/74, Group 2: 1/74; Comments: 0.539 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: headache at postoperatively; Group 1: 0/74, Group 2: 2/74; Comments: 0.637 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Forrest 2002[302]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=11245)
Countries and setting	Conducted in Belgium, Finland, Irish Republic, Italy, Portugal, Spain, Switzerland, United Kingdom; Setting: 49 hospitals in eight countries in Europe
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>18 years old undergoing elective major surgery
Exclusion criteria	known sensitivity to any study medications or other NSAIDs, patients in whom NSAIDs were contraindicated, who were pregnant or lactating, who were to undergo minor surgery, emergency or day case surgery or were ASA V

Recruitment/selection of patients	undergoing elective major surgery
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 48 ± 17; Diclofenac: 47 ± 17. Gender (M:F): 2244/2923. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 48 ± 17; Diclofenac: 47 ± 17). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I:3191, ASA II 1531, ASA III 421, ASA IV 24). 3. Type of surgery: Not applicable (Orthopaedic 904; Abdominal 428; Plastics/ENT 1188; Gynaecology 1059; Urology 592; Other 1025). 4. Ketorolac 90mg; Diclofenac 150mg.
Indirectness of population	--
Interventions	(n=2585) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. ketorolac, parenteral 90 mg day for 2 days followed by oral 40 mg day for up to 7 days;. Duration unspecified . Concurrent medication/care: If additional analgesia was required, an opioid could be used. Indirectness: No indirectness (n=2582) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. diclofenac, parenteral 150 mg day for 2 days followed by oral 150 mg day for up to 7 days. Duration unspecified. Concurrent medication/care: If additional analgesia was required, an opioid could be used. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (UK medicines control agency and the committee for proprietary medicinal products in europe)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Mortality at Postoperatively; Group 1: 9/2576, Group 2: 5/2568
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 14
- Actual outcome: Surgical Site Bleed at Postoperatively; Group 1: 39/2576, Group 2: 37/2568; Comments: p value 0.83
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 14
- Actual outcome: GI bleed at Postoperatively; Group 1: 0/2576, Group 2: 1/2568; Comments: p value 0.50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 14
- Actual outcome: Allergic reaction at Postoperatively; Group 1: 3/2576, Group 2: 3/2568; Comments: p value 1
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 14
- Actual outcome: Other adverse events at Postoperatively; Group 1: 75/2576, Group 2: 82/2568; Comments: p value 0.56
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9; Group 2 Number missing: 14 - Actual outcome: Acute renal failure at Postoperatively; Group 1: 2/2576, Group 2: 4/2568; Comments: p value 0.45 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 14	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Fredman 1995[305]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Israel; Setting: Medical university hospital, Israel
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II undergoing laparoscopic cholecystecomy
Exclusion criteria	history of peptic ulcer disease, bleeding disorders, current anticoagulant therapy or regular NSAIDs / psychotropic drugs
Recruitment/selection of patients	undergoing laparoscopic cholecystecomy
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 48 (16); Diclofenac: 55 (14). Gender (M:F): 9/30. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 48 (16); Diclofenac: 55 (14)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (cholecystectomy). 4. Ketorolac 60mg; Diclofenac 75mg.
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. Thirty minutes prior to the end of surgery, patients received Ketorolac 60mg IM. Duration single administration. Concurrent medication/care: PCA

	device programmed to deliver 1mg bolus of morphine with a 6 minute lock out interval with no basal infusion. (n=20) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. Thirty minutes prior to the end of surgery, patients received Diclofenac 75mg IM. Duration single administration. Concurrent medication/care: PCA device programmed to deliver 1mg bolus of morphine with a 6 minute lock out interval with no basal infusion.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain score at ≤ 4 hours postoperatively; Group 1: mean 2 (SD 2); n=19, Group 2: mean 3 (SD 1); n=20; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: Cumulative morphine consumption at ≤ 4 hours postoperatively; Group 1: mean 8.6 milligrams (SD 5.2); n=19, Group 2: mean 8.9 milligrams (SD 4.8); n=20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Fricke 1993[308]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=207)
Countries and setting	Conducted in USA; Setting: Austin Oral Surgery, Texas, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>15 in good health, and experiencing at least moderate pain after surgical extraction of three or four third molars at least one of which was a mandibular partial or complete bony extraction.
Exclusion criteria	Patients who had ingested aspirin, acetominophen, or short acting NSAIDS within 12 hours, long acting NSAIDs within 48 hours, or steroids within 72 hours were excluded. ALso excluded were patients who received parenteral or oral anesthesia, sedatives, or other mood altering drugs.
Recruitment/selection of patients	Enrolled from those patients who have moderate postoperative pain after extraction of three or four third molars
Age, gender and ethnicity	Age - Mean (SD): Naproxen: 24.1 (6.8); Ibuprofen: 22.5 (4.5). Gender (M:F): 64/98. Ethnicity: NA
Further population details	1. Age: <60 years (Naproxen: 24.1 (6.8); Ibuprofen: 22.5 (4.5)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (Dental surgery). 4. Naproxen 440mg; Ibuprofen 400mg.
Indirectness of population	--
Interventions	(n=81) Intervention 1: Non-steroidal anti-inflammatory - Naproxen. Patients were instructed to take dose of study drug for moderate pain. Patients received Naproxen Sodium 440mg. Duration single dose. Concurrent medication/care: Patients were instructed to take additional pain relief as needed, however, which pain relief to take has not been specified in protocol. . Indirectness: Serious indirectness; Indirectness comment: rescue analgesia not specified (n=81) Intervention 2: Non-steroidal anti-inflammatory - Ibuprofen. Patients were instructed to take dose of study drug for moderate pain. Patients received Ibuprofen 400mg. Duration single dose. Concurrent medication/care: Patients were instructed to take additional pain relief as needed, however, which pain relief to take has not been specified in protocol. . Indirectness: Serious indirectness; Indirectness comment: rescue analgesia not specified
Funding	Other (Unclear - mention of Pharmaco LSR Texas)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus IBUPROFEN

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: TOTPAR at 6 hours postoperatively; Group 1: mean 11.6 (SD 8-.5); n=81, Group 2: mean 10.9 (SD 8.4); n=81; Comments: p value 0.586
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: TOTPAR at 12 hours postoperatively; Group 1: mean 19.6 (SD 17.3); n=81, Group 2: mean 15.8 (SD 14.8); n=81; Comments: p value 0.103 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Pain relief (50% resolved) at Postoperatively; Group 1: mean 0.4 (SD 0.4); n=81, Group 2: mean 0.4 (SD 0.3); n=81; Comments: p value 0.267 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Gan 2012[315]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=348)
Countries and setting	Conducted in USA; Setting: Duke University Medical Center, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	scheduled for abdominal or pelvic surgery
Age, gender and ethnicity	Age - Mean (SD): Mean age: 43. Gender (M:F): Define. Ethnicity: NA

Further population details	1. Age: <60 years (Mean age: 43). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (abdominal or pelvic surgery). 4. Diclofenac 18.75 – 37.5mg; Ketorolac 30mg.
Indirectness of population	No indirectness
Interventions	(n=173) Intervention 1: Non-steroidal anti-inflammatory - Diclofenac. diclofenac 18.75 mg or 37.5 mg. The first dose of study medication (1 mL IV bolus) was received by patients in all treatment arms within this first 6-hour period. Subsequent injections were received every 6 hours until discharge or until patient withdrawal/ discontinuation from the study.. Duration postoperatively up to 5 days . Concurrent medication/care: Rescue medication (bolus IV morphine 5 mg, titrated up to 7.5 mg after 30 min if analgesia was inadequate) was available upon patient request, up to once every 3 hours any time after administration of the initial dose of study drug. . Indirectness: No indirectness (n=82) Intervention 2: Non-steroidal anti-inflammatory - Ketorolac. ketorolac tromethamine Ketorolac tromethamine 30 mg. The first dose of study medication (1 mL IV bolus) was received by patients in all treatment arms within this first 6-hour period. Subsequent injections were received every 6 hours until discharge or until patient withdrawal/ discontinuation from the study.. Duration postoperatively up to 5 days. Concurrent medication/care: Rescue medication (bolus IV morphine 5 mg, titrated up to 7.5 mg after 30 min if analgesia was inadequate) was available upon patient request, up to once every 3 hours any time after administration of the initial dose of study drug. . Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Javelin Pharmaceuticals, Inc., Cambridge, MA (now Hospira, Inc., Lake Forest, IL following acquisition in 2010).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Nausea at postoperatively; Group 1: 22/67, Group 2: 48/141
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: lack of efficacy, subject request, lost to follow up, adverse event, other; Group 2 Number missing: 32, Reason: lack of efficacy, subject request, lost to follow up, adverse event, other
- Actual outcome: Headache at postoperatively; Group 1: 14/67, Group 2: 16/141
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: lack of efficacy, subject request, lost to follow up, adverse event, other; Group 2 Number missing: 32, Reason: lack of efficacy, subject request, lost to follow up, adverse event, other
- Actual outcome: Vomiting at postoperatively; Group 1: 7/67, Group 2: 12/141
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: lack of efficacy, subject request, lost to follow up, adverse event, other; Group 2 Number missing: 32, Reason: lack of efficacy, subject request, lost to follow up, adverse event, other - Actual outcome: Pruritis at postoperatively; Group 1: 3/67, Group 2: 10/141 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15, Reason: lack of efficacy, subject request, lost to follow up, adverse event, other; Group 2 Number missing: 32, Reason: lack of efficacy, subject request, lost to follow up, adverse event, other	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Jakobsson 1996[437]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=200)
Countries and setting	Conducted in Sweden; Setting: Danderyds Hospital, Sweden
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I scheduled for minor gynecological surgery
Exclusion criteria	not specified
Recruitment/selection of patients	scheduled for minor gynecological surgery
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 26 (7); Diclofenac: 25 (6). Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: >60 years (Ketorolac: 26 (7); Diclofenac: 25 (6)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 3. Type of surgery: gynae-oncology (minor gynecological surgery). 4. Ketorolac 30mg; Diclofenac 75mg.
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. 30mg Ketorolac IM given 10 - 20 minutes

	before anesthesia . Duration Single administration. Concurrent medication/care: Paracetamol 1g was administered rectally as pain relief when requested. If insufficient 3 - 5 mg of IV morphine was administered. . Indirectness: No indirectness (n=50) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. 75mg Diclofenac IM given 10 - 20 minutes before anesthesia . Duration Single administration. Concurrent medication/care: Paracetamol 1g was administered rectally as pain relief when requested. If insufficient 3 - 5 mg of IV morphine was administered. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea at postoperatively; Group 1: 2/50, Group 2: 0/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 1/50, Group 2: 3/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Length of hospital stay - Actual outcome: Time to discharge at postoperatively; Group 1: mean 107 minutes (SD 27); n=50, Group 2: mean 109 minutes (SD 27); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Hospital readmission

Study	**Joshi 2004[464]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	(n=125)
Countries and setting	Conducted in United Kingdom; Setting: University Dental Hospital, Manchester UK
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II who were to have third molar teeth removed under general anesthesia
Exclusion criteria	Not specified
Recruitment/selection of patients	third molar teeth removed under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Mean age: 26 (6). Gender (M:F): Unclear. Ethnicity: NA
Further population details	1. Age: <60 years (Mean age: 26 (6)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: Not applicable (Dental surgery). 4. Diclofenac 100mg; Ibuprofen 600mg.
Indirectness of population	--
Interventions	(n=29) Intervention 1: Non-steroidal anti-inflammatory - Diclofenac. Diclofenac 100mg given preoperatively. Duration Single administration. Concurrent medication/care: 1g of paracetamol and codeine 30mg once in 6h (maximum 8 tablets a day). Indirectness: No indirectness (n=31) Intervention 2: Non-steroidal anti-inflammatory - Ibuprofen. Ibuprofen 600mg given 1 hour preoperatively. Duration single administration. Concurrent medication/care: 1g of paracetamol and codeine 30mg once in 6h (maximum 8 tablets a day). Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus IBUPROFEN

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score at 3 hours postoperatively; Median (range): Diclofenac: 33 (0-100); Ibuprofen: 31 (0-100));
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Kiersch 1993[509]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=203)
Countries and setting	Conducted in USA; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>15 years of age; experiencing at least moderate pain following extraction of one or two bony impacted third molars
Exclusion criteria	Pregnant or lactating women not using adequate contraception. Patients who receieved parenteral or oral anesthesia or who had taken any sedatives, acetominophen, short acting NsIDs within 48 hours of surgery were also excluded. Patients with a known history of allergy or serious adverse reactions to study medications.
Recruitment/selection of patients	experiencing at least moderate pain following extraction of one or two bony impacted third molars
Age, gender and ethnicity	Age - Mean (SD): Naproxen: 25.4 (6.9); Ibuprofen; 24.9 (6.3). Gender (M:F): 71/90. Ethnicity: NA
Further population details	1. Age: <60 years (Naproxen: 25.4 (6.9); Ibuprofen; 24.9 (6.3)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable 3. Type of surgery: Not applicable (Dental surgery). 4. Naproxen 220mg; Ibuprofen 200mg.
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Non-steroidal anti-inflammatory - Naproxen. Naproxen sodium 220mg following dental surgery when patients are experiencing moderate pain after extraction. Duration single administration. Concurrent medication/care: Rescue analgesia not specified. . Indirectness: Serious indirectness;

	Indirectness comment: Rescue analgesia not specified. (n=81) Intervention 2: Non-steroidal anti-inflammatory - Ibuprofen. Ibuprofen 200mg following dental surgery when patients are experiencing moderate pain after extraction. Duration single administration. Concurrent medication/care: Rescue analgesia not specified. . Indirectness: Serious indirectness; Indirectness comment: Rescue analgesia not specified.
Funding	Study funded by industry (Study was supported by a research grant from Syntex Laboratories, California)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus IBUPROFEN Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: TOTPAR at 6 hours postoperatively; Group 1: mean 11.7 (SD 7.8); n=80, Group 2: mean 10.3 (SD 8.1); n=81; Comments: p value 0.292 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0 Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: TOTPAR at 12 hours postoperatively; Group 1: mean 21.3 (SD 16.5); n=80, Group 2: mean 17.8 (SD 15.8); n=81; Comments: p value 0.146 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Kostamovaara 1998[548]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=85)
Countries and setting	Conducted in Finland; Setting: Kuopio University Hospital, Kuopio, Finland
Line of therapy	Adjunctive to current care

Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I–III patients, aged 45–81 yr, undergoing total hip replacement surgery
Exclusion criteria	Patients with hypersensitivity to anti-inflammatory drugs, asthma, clinical hepatic or renal failure, bleeding or coagulation disorders, gastrointestinal ulceration or dyspepsia were excluded
Recruitment/selection of patients	undergoing total hip replacement surgery
Age, gender and ethnicity	Age - Median (range): Ketorolac: 65 (54-80); Diclofenac 60 (45-77). Gender (M:F): 31/25. Ethnicity: NA
Further population details	1. Age: >60 years (Ketorolac: 65 (54-80); Diclofenac 60 (45-77)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I - III). 3. Type of surgery: ortho/large joint replacement (total hip replacement surgery). 4. Ketorolac 30mg; Diclofenac 75mg.
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. ketorolac 30 mg as an i.v. loading dose for 30 min followed by infusion of ketorolac 90 mg over 15.5 h. Duration 15.5 hours postoperatively. Concurrent medication/care: PCA fentanyl 50 µg i.v : infusion time was 5 min, lock-out time was 5 min and maximum dose was 300 µg h-1. Indirectness: No indirectness (n=28) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. diclofenac 75 mg i.v. loading dose for 30 min followed by infusion of diclofenac 75 mg over 15.5 h. Duration 15.5 hours postoperatively. Concurrent medication/care: PCA fentanyl 50 µg i.v : infusion time was 5 min, lock-out time was 5 min and maximum dose was 300 µg h-1. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Mean fentanyl consumption at 0-5h; Group 1: mean 60 micrograms (SD 40); n=28, Group 2: mean 60 micrograms (SD 30); n=28
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Mean fentanyl consumption at 10-16h; Group 1: mean 50 micrograms (SD 30); n=28, Group 2: mean 40 micrograms (SD 30); n=28 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea at Postoperatively; Group 1: 9/28, Group 2: 9/28 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at Postoperatively; Group 1: 9/28, Group 2: 5/28 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Itching at Postoperatively; Group 1: 4/28, Group 2: 3/28 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Leykin 2008[606]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Italy; Setting: Tertiary hospital, Italy
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients ASA I - II, aged 18 - 65, undergoing functional endoscopic sinus surgery / Turbinate surgery

Exclusion criteria	unable to cooperate, had a history of GI bleeding, impaired liver function, or renal function, history of drug or alcohol abuse, chronic pain or known allergy to study medications.
Recruitment/selection of patients	undergoing functional endoscopic sinus surgery / Turbinate surgery
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 35 (11); Parecoxib: 32 (10). Gender (M:F): 39/11. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 35 (11); Parecoxib: 32 (10)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: Not applicable (ENT surgery: functional endoscopic sinus surgery / Turbinate surgery). 4. Ketorolac 30mg; Parecoxib 40mg.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. 30mg of Ketorolac 15 minutes prior to the end of intraoperative remifentanil infusion . Duration Single administration. Concurrent medication/care: Rescue analgesia was given via IV morphine 2mg at 10 minute intervals until pain was resolved and 2g IV proparacetamol once left from PACU. Indirectness: No indirectness (n=25) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. 40mg of Parecoxib 15 minutes prior to the end of intraoperative remifentanil infusion . Duration single administration. Concurrent medication/care: Rescue analgesia was given via IV morphine 2mg at 10 minute intervals until pain was resolved and 2g IV proparacetamol once left from PACU. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score - area under the curve at 6 hours post surgery; Median (range): Ketorolac: 1.858 (0.078 - 5.281); Parecoxib: 1.764 (0.072-3.925), Comments: p value not significant);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain score - area under the curve at 24 hours post surgery; Median (range): Ketorolac: 2.306 (1.285-4.434); Parecoxib: 1.986 (0.875-3.889), Comments: p value not significant);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Morphine consumption in PACU at 6 hours post surgery;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea and vomiting at up to 24 hours post surgery; Group 1: 1/25, Group 2: 2/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Gastric pain at up to 24 hours post surgery; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Manvelian 2012[664]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=202)
Countries and setting	Conducted in USA; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	≥18 years of age, had a body weight >45 kg, and a body mass index ≥ 35 kg/m2, if female, were not pregnant or lactating and practicing an acceptable form of birth control or not of childbearing potential (e.g., hormonal methods, abstinence, intrauterine device, double-barrier method), were in good health
Exclusion criteria	A subject was not eligible for study entry if they had a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, or any NSAIDs, had a positive drug test during screening, had a history of a clinically significant GI event □6 months before screening or had any history of peptic or gastric ulcers or GI bleeding, had

	a surgical or medical condition of the GI or renal system that might have significantly altered the absorption, distribution, or excretion of any drug substance, had a history of chronic NSAID, opioid, or glucocorticoid use, had a significant renal or hepatic disease, had difficulty swallowing capsules/oral medication, or previously participated in a clinical study involving nano-formulated diclofenac.
Recruitment/selection of patients	subjects with acute dental pain after third molar extraction
Age, gender and ethnicity	Age - Mean (SD): Diclofenac: 22.2 ± 4.9; Celecoxib: 22.7 ± 3.3. Gender (M:F): 60/91. Ethnicity: NA
Further population details	1. Age: <60 years (Diclofenac: 22.2 ± 4.9; Celecoxib: 22.7 ± 3.3). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (Dental surgery). 4. Diclofenac 18 – 35mg; Celecoxib 400mg.
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Non-steroidal anti-inflammatory - Diclofenac. nano-formulated diclofenac 18 mg OR nano-formulated diclofenac 35 mg in subjects who experienced moderate to severe pain intensity (a score of ≥ 50 mmon a 100 mmVAS) within 6 hours after surgery. Duration not specified . Concurrent medication/care: Subjects were encouraged to wait at least 60 minutes after receiving study drug before taking the protocol specified rescue medication, acetaminophen 1,000 mg. Additional analgesic rescue medications were administered at the discretion of the investigator if acetaminophen was deemed inadequate.. Indirectness: No indirectness (n=51) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Celecoxib 400mg in subjects who experienced moderate to severe pain intensity (a score of ≥ 50 mmon a 100 mmVAS) within 6 hours after surgery. Duration not specified. Concurrent medication/care: Subjects were encouraged to wait at least 60 minutes after receiving study drug before taking the protocol specified rescue medication, acetaminophen 1,000 mg. Additional analgesic rescue medications were administered at the discretion of the investigator if acetaminophen was deemed inadequate.. Indirectness: No indirectness
Funding	Funding not stated (Two lead authors are consultants or part of Iroko Pharmaceuticals and the third an employee of Premier research group International, which was contacted to complete this Phase 2 clinical trial.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus CELECOXIB

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: TOTPAR at 4 hours postoperatively; Group 1: mean 8.12 (SD 4.3); n=100, Group 2: mean 5.71 (SD 5.01); n=51
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: TOTPAR at 12 hours postoperatively; Group 1: mean 17.3 (SD 13.27); n=100, Group 2: mean 14.61 (SD 15.05); n=51 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Mehlisch 2003[697]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=457)
Countries and setting	Conducted in USA; Setting: SCIREX corporation clinical site, Texas, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged ≥18, in good health and who had undergone surgical extraction of 2 or more impacted third molars (one of which was mandibular) requiring bone removal and were experiencing moderate to severe pain within 6 hours of surgery.
Exclusion criteria	History of upper Gi ulceration within 6 months, uncontrolled chronic disease, nasal polyps, NSAID induced bronchospasm or angiodema, known hypersensitivity to study medications, chronic analgesia usage or substance abuse.
Recruitment/selection of patients	undergone surgical extraction of 2 or more impacted third molars
Age, gender and ethnicity	Age - Other: Mean age: Ketorolac: 22.5; Parecoxib: 23.6. Gender (M:F): 61/142. Ethnicity: NA
Further population details	1. Age: <60 years (Mean age: Ketorolac: 22.5; Parecoxib: 23.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (Dental surgery). 4.

	Ketorolac 30mg; Parecoxib 20 – 100mg.
Indirectness of population	--
Interventions	(n=50) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. 30mg of Ketorolac, within 6 hours of surgery completion and having moderate or severe postoperative pain.. Duration Single administration. Concurrent medication/care: Rescue medications were available as follows: Acetominophen PO 1000mg; Lortab PO (Hydrocodone 5mg + acetominophen 500mg) Lortab PO (Hydrocodone 7.5mg + acetominophen 500mg) Demerol (IM - Meperidine 50mg) Phenergan (25mg Promethazine). Indirectness: No indirectness (n=153) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. 20mg, 50mg, or 100mg or Parecoxib, within 6 hours of surgery completion and having moderate or severe postoperative pain.. Duration Single administration. Concurrent medication/care: Rescue medications were available as follows: Acetominophen PO 1000mg; Lortab PO (Hydrocodone 5mg + acetominophen 500mg) Lortab PO (Hydrocodone 7.5mg + acetominophen 500mg) Demerol (IM - Meperidine 50mg) Phenergan (25mg Promethazine). Indirectness: No indirectness
Funding	Study funded by industry (Study funded by Pharmacia corporation, Texas)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Abdominal pain at Postoperatively; Group 1: 1/50, Group 2: 1/153
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: infiltration of study medication into wound; Group 2 Number missing: 1, Reason: infiltration of study medication into wound
- Actual outcome: headache at Postoperatively; Group 1: 6/50, Group 2: 12/153
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: infiltration of study medication into wound; Group 2 Number missing: 1, Reason: infiltration of study medication into wound
- Actual outcome: nausea at Postoperatively; Group 1: 13/50, Group 2: 23/153
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: infiltration of study medication into wound; Group 2 Number

missing: 1, Reason: infiltration of study medication into wound - Actual outcome: vomiting at Postoperatively; Group 1: 4/50, Group 2: 9/153 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: infiltration of study medication into wound; Group 2 Number missing: 1, Reason: infiltration of study medication into wound	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Mehlisch 2004[698]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=353)
Countries and setting	Conducted in USA; Setting: SCIREX facilities (drug development organization Texas)
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 - 45 years, undergoing surgical extraction of two or more impacted third molars requiring bone removal. To be recruited patients were required to have moderate to severe pain intensity within the first 6 hours after surgery.
Exclusion criteria	uncontrolled chronic disease or any laboratory abnormalities that could contraindicate participation. Patients were also excluded if they had GI ulceration within 6 months prior to the procedure, or a history of nasal polyps and or a history of angioedema and bronchospasm caused by NSAIDs; used analgesics or other agents during the 6 hours preceding dental surgery
Recruitment/selection of patients	undergoing surgical extraction of two or more impacted third molars requiring bone removal
Age, gender and ethnicity	Age - Other: mean age: Ketorolac: 24; Parecoxib: 23.8. Gender (M:F): 69/82. Ethnicity: NA
Further population details	1. Age: <60 years (mean age: Ketorolac: 24; Parecoxib: 23.8). 2. American Society of Anesthesiologists

	(ASA) Physical Status grade: Not applicable 3. Type of surgery: Not applicable (Dental surgery). 4. Ketorolac 30mg; Parecoxib 20mg.
Indirectness of population	--
Interventions	(n=51) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. Ketorolac 30mg IM if pain was ≥50mm on VAS within 6 hours after surgery. Duration single administration. Concurrent medication/care: Oral acetaminophen 1,000 mg, oral hydrocodone 5 mg, plus acetaminophen 500 mg, oral hydrocodone 7.5 plus acetominophen 500mg or IM meperidine 50 mg plus promethazine 25mg . Indirectness: No indirectness (n=50) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Parecoxib 20mg IM if pain was ≥50mm on VAS within 6 hours after surgery. Duration single administration. Concurrent medication/care: Oral acetaminophen 1,000 mg, oral hydrocodone 5 mg, plus acetaminophen 500 mg, oral hydrocodone 7.5 plus acetominophen 500mg or IM meperidine 50 mg plus promethazine 25mg . Indirectness: No indirectness
Funding	Study funded by industry (Study funded by Pfizer pharmaceutical and Pharmacia corporation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: TOTPAR at 6 hours postoperatively; Group 1: mean 14.6 (SD 7.36); n=51, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: protocol violation; Group 2 Number missing: Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: TOTPAR at 24 hours postoperatively; Group 1: mean 39.4 (SD 26.2); n=51, Group 2: mean 47 (SD 33.9); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: protocol violation; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Mony 2016[747]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in India; Setting: Dr. D.Y. Patil Dental College and Hospital, India
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with bilateral impacted third molar with similar difficulty index in healthy young adults of both genders belonging to age group of 20– 30 years, willing to give written informed consent were included
Exclusion criteria	patients with infection, systemic condition, on anti-inflammatory and on anticoagulant therapy. The study was conducted with institutional ethical board clearance and all patients written informed consent for the surgical procedure were obtained.
Recruitment/selection of patients	bilateral impacted third molar with similar difficult
Age, gender and ethnicity	Age - Other: mean age: 26.44. Gender (M:F): unspecified. Ethnicity: NA
Further population details	1. Age: <60 years (mean age: 26.44). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable 3. Type of surgery: Not applicable (Dental surgery). 4. Ketorolac 30mg; Diclofenac 75mg.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. received 30mg ketorolac intramuscular injection 30 minutes preoperatively in the deltoid region. Duration preoperatively. Concurrent medication/care: ibuprofen 400mg for rescue medication. Indirectness: No indirectness (n=25) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. received 75mg diclofenac sodium intramuscular injection 30 minutes preoperatively in the deltoid region.. Duration preoperatively. Concurrent medication/care: ibuprofen 400mg for rescue medication. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain score at ≤6 hours postoperatively; Group 1: mean 1 pain score (SD 1.088); n=25, Group 2: mean 0.78 pain score (SD 0.887); n=25; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.237 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: Pain score at 12 hours postoperatively; Group 1: mean 0.14 pain score (SD 0.405); n=25, Group 2: mean 0.25 pain score (SD 0.573); n=25; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.134 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Morrow 1993[757]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=71)
Countries and setting	Conducted in Irish Republic; Setting: Musgrave Park Hospital, Northern Ireland
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(ASA 1-2) patients aged 18-60 years scheduled for elective day case arthroscopy of the knee joint.
Exclusion criteria	Patients with a history of gastric bleeding, renal impairment,

	concurrent NSAID therapy, a history of major medical illness or a known intolerance to NSAIDS were not studied.
Recruitment/selection of patients	scheduled for elective day case arthroscopy of the knee joint.
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 30 (9.5); Diclofenac: 32 (10.7). Gender (M:F): 59/12. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 30 (9.5); Diclofenac: 32 (10.7)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: ortho/large joint replacement (Knee arthroscopy). 4. Ketorolac 30mg; Diclofenac 75mg.
Indirectness of population	--
Interventions	(n=36) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. single deep intramuscular injection of ketorolac 30 mg into the upper outer quadrant of the buttock of the non-operated leg.. Duration preoperatively. Concurrent medication/care: Postoperative analgesia was provided either in the form of intramuscular morphine (Cyclimorph '10') or oral paracetemol/codeine (Paracodol) at the discretion of the recovery ward staff who were unaware of the nature of the intra-operative analgesia.. Indirectness: No indirectness (n=35) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. single deep intramuscular injection of diclofenac 75 mg into the upper outer quadrant of the buttock of the non-operated leg.. Duration preoperatively. Concurrent medication/care: Postoperative analgesia was provided either in the form of intramuscular morphine (Cyclimorph '10') or oral paracetemol/codeine (Paracodol) at the discretion of the recovery ward staff who were unaware of the nature of the intra-operative analgesia.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain score at 4 hours postoperatively; Group 1: mean 1.55 pain score (SD 1.76); n=36, Group 2: mean 1.7 pain score (SD 1.79); n=35; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.73 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale

	(HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study (subsidiary papers)	**NCT03331315 trial: Ulm 2017[1284] (Ulm 2018[1285])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=138)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention): 24 hour and 2 week post-surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People having had robotic hysterectomy
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	People undergoing robotic hysterectomy
Exclusion criteria	Preoperative pain scores of less than 3/10, chronic opioid use (>21 days), crohn's disease, ulcerative colitis, peptic ulcer disease, recent myocardial infarction of stroke (within last 6 months), allergy to NSAIDs, preoperative hematocrit <24, platelet count of less than 100,000, sulfa allergy or preoperative creatinine >1.5.
Age, gender and ethnicity	Age - Mean (SD): Ketorolac group: 56.3 (11.3), celebrex group: 55.1 (14.4)). Gender (M:F): Not specifed. Ethnicity: NA Not stated
Further population details	1. Age: <60 years (mean age reported). 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Type of surgery: gynae-oncology (Hysterectomy). 4. Ketorolac 30mg; Celecoxib 200-400mg.
Indirectness of population	Serious indirectness: people in the ketorolac arm received this treatment perioperatively
Interventions	(n=70) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. Ketorolac during surgery 30 mg intravenous and then 6 hourly for 48 hours or until discharge. . Duration 48 hours or until discharge. Concurrent medication/care: Scheduled preoperative and postoperative Tylenol (975 mg PO q 8 hours) and Gabapentin (100 mg PO q 8 hours) as well as postoperative intravenous and oral narcotics as needed. . Indirectness: Serious indirectness; Indirectness comment: treatment administered perioperatively as apposed to postoperatively and continued postoperatively (n=68) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Celecoxib 1 hour before surgery at 400 mg and followed by postoperative oral celecoxib 200 mg twice daily for 7 days following discharge. .

	Duration 7 days postoperatively. Concurrent medication/care: Scheduled preoperative and postoperative Tylenol (975 mg PO q 8 hours) and Gabapentin (100 mg PO q 8 hours) as well as postoperative intravenous and oral narcotics as needed. . Indirectness: Serious indirectness; Indirectness comment: Initially taken preoperatively and then taken after discharge.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus CELECOXIB Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain score (average) at during first 24 hours postoperative; Group 1: mean 2.7 (SD 1.9); n=70, Group 2: mean 2.4 (SD 1.6); n=68 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Ketoprofen taken during surgery with no details on duration; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Dilaudid (mg) at during first 24 hours postoperative; Group 1: mean 0.7 mg (SD 1); n=70, Group 2: mean 0.8 mg (SD 1); n=68 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Ketoprofen taken during surgery with no details on duration; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Morphine (mg) at during first 24 hours postoperative; Group 1: mean 0.5 mg (SD 2.1); n=70, Group 2: mean 0.4 mg (SD 1.6); n=68 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Ketoprofen taken during surgery with no details on duration; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Oxycodone (mg) at during first 24 hours postoperative; Group 1: mean 4 mg (SD 6.9); n=70, Group 2: mean 5.4 mg (SD 9); n=68 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Ketorolac taken during surgery with no details on duration; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Ng 2004[912]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=36)
Countries and setting	Conducted in United Kingdom; Setting: Leicester Royal Infirmary
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	20-50 yr and undergoing laparoscopic sterilization
Exclusion criteria	Patients with a chronic pain syndrome or receiving regular analgesics were excluded.
Recruitment/selection of patients	undergoing laparoscopic sterilization
Age, gender and ethnicity	Age - Mean (range): Ketorolac: 35 (32-38); Parecoxib: 34 (29-38). Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 35 (32-38); Parecoxib: 34 (29-38)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 31; ASA II: 4). 3. Type of surgery: gynae-oncology (laparoscopic sterilization). 4. Ketorolac 30mg; Parecoxib 40mg.
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. ketorolac 30 mg i.v., at induction of anesthesia.. Duration preoperatively. Concurrent medication/care: patients were asked if they needed rescue analgesia, which comprised two tablets of cocodamol 30/500 (codeine phosphate 30 mg, acetaminophen 500 mg) for mild to moderate pain, and morphine 10 mg i.m. for severe pain. Indirectness: No indirectness (n=18) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. parecoxib 40 mg i.v. at induction of anaesthesia.. Duration preoperatively. Concurrent medication/care: patients were asked if they needed rescue analgesia, which comprised two tablets of cocodamol 30/500 (codeine phosphate 30 mg, acetaminophen 500 mg) for mild to moderate pain, and morphine 10 mg i.m. for severe pain. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Pharmacia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score at 3 hours postoperatively; Median (IQR): Ketorolac:11 (1-28); Parecoxib: 5 (0-28), Comments: p value 0.01);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: protocol violation; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Nausea at 3 hours postoperatively; Median (IQR): Ketorolac: 2 (0-5); Parecoxib: 0 (0-0), Comments: p value 0.121);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: protocol violation; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Perttunen 1999[997]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Finland; Setting: Helsinki University Central Hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I–III adult patients, less than 75 yr of age
Exclusion criteria	Patients with cardiac, renal or hepatic failure were excluded, as were those with a history of gastrointestinal bleeding or peptic ulceration, haemorrhagic diathesis and asthma, or allergy to acetosalicylic acid or other non-steroidal anti-inflammatory analgesics or morphine. Con- fused patients, those with a preoperative forced expiratory volume in 1s (FEV1) of less than 60% of the reference value and patients with sleep apnoea were also excluded.

Recruitment/selection of patients	patients undergoing video-assisted thoracoscopic surgery and receiving a 2-day i.v. infusion of diclofenac, ketorolac
Age, gender and ethnicity	Age - Mean (range): Ketorolac: 40.6 (18–64); Diclofenac: 50.3 (26–70). Gender (M:F): 9/11. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 40.6 (18–64); Diclofenac: 50.3 (26–70)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 6; ASA II: 11; ASA III: 3). 3. Type of surgery: Not applicable (video-assisted thoracoscopic surgery (VATS)). 4. Ketorolac variable dose; Diclofenac variable dose.
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. The ketorolac infusion (0.6 mg ml–1 in 0.9% NaCl) was started with a bolus dose of 17 ml (=10 mg) in 30 min and continued with a constant rate of 2 ml kg–1/24 h for 48 h. The maximum daily dose was 90 mg. . Duration 48 hours postoperatively. Concurrent medication/care: All patients were allowed supplementary doses of morphine 2 mg ml–1 i.v. from a patient-controlled analgesia (PCA) device. The PCA device was programmed to provide a bolus dose of 30g/kg–1. The lockout time was 5–10 min until the first postoperative morning and thereafter 10–12 min. . Indirectness: No indirectness (n=10) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. The diclofenac infusion (1 mg ml–1 in 0.9% NaCl) was started with a bolus dose of 17 ml (=17 mg) in 30 min and continued with a constant rate of 2 ml kg–1/24 h for 48 h.. Duration 48 hours postoperatively. Concurrent medication/care: All patients were allowed supplementary doses of morphine 2 mg ml–1 i.v. from a patient-controlled analgesia (PCA) device. The PCA device was programmed to provide a bolus dose of 30g/kg–1. The lockout time was 5–10 min until the first postoperative morning and thereafter 10–12 min. . Indirectness: No indirectness
Funding	Academic or government funding (Financial support of the Helsinki University Central Hospital Research Fund and Helsinki University)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Amount of additional medication use (>6-24 hours post op) - Actual outcome: mean cumulative morphine consumption at 20 hours postoperatively; Group 1: mean 31.6 milligrams (SD 32.4); n=10, Group 2: mean 21 milligrams (SD 4); n=10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac

	events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Siribumrungwong 2015[1165]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=66)
Countries and setting	Conducted in Thailand; Setting: Prince of Songkla University, Thailand
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients who were diagnosed as lumbar disc herniation, spondylolisthesis, spinal stenosis, and had indications for decompressive laminectomy and fusion for one to three levels; 18–80 years; ASA of I-II
Exclusion criteria	Exclusion criteria were a history of NSAIDs or opioid or sulfonamide allergy, any coagulopathy disease or patients who current use of antiplatelet or anticoagulant drugs, severe hepatic impairment, acute peptic ulceration, congestive heart failure, pregnancy, and lactation.
Recruitment/selection of patients	Indications for decompressive laminectomy and fusion for one to three levels
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 58.2 ± 9.5; Parecoxib: 58 ± 8.6. Gender (M:F): 20/44. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 58.2 ± 9.5; Parecoxib: 58 ± 8.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I: 20: ASA II: 44). 3. Type of surgery: ortho/large joint replacement (decompressive laminectomy and fusion). 4. Ketorolac 30mg; Parecoxib 40mg.
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. the ketorolac group received 30 mg of ketorolac intravenously. All patients received their medication 30 minutes before surgery from the anesthesiologist.. Duration preoperatively. Concurrent medication/care: All patients received the same postoperative pain management, consisting of paracetamol (500 mg) and intravenous morphine for rescue postoperative pain control. No other analgesic supplement was given during the study period.. Indirectness:

	No indirectness (n=32) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. The parecoxib group received 40 mg of parecoxib intravenously. All patients received their medication 30 minutes before surgery from the anesthesiologist.. Duration preoperatively. Concurrent medication/care: All patients received the same postoperative pain management, consisting of paracetamol (500 mg) and intravenous morphine for rescue postoperative pain control. No other analgesic supplement was given during the study period.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score at 6 hours postoperatively; Group 1: mean 5.7 (SD 2.34); n=32,
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score at 24 hours postoperatively; Group 1: mean 4.7 (SD 2.05); n=32,
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine consumption at 24 hours postoperatively; Group 1: mean 6.4 milligrams (SD 7); n=32, Group 2: mean 4.9 milligrams (SD 4.6); n=32; Comments: p value 0.55
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Nausea and vomiting at postoperatively; Group 1: 12/32, Group 2: 11/32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures

	(including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Tarkkila 1996[1244]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=0)
Countries and setting	Conducted in Finland; Setting: Department of Surgery, University of Helsinki, Finland
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients ASA I-II patients scheduled for maxillofacial surgery
Exclusion criteria	Patients with a history of allery to NSAIDs, broncial asthma, GI ulceration or bleeding disorders were excluded
Recruitment/selection of patients	scheduled for maxillofacial surgery
Age, gender and ethnicity	Age - Mean (SD): ketorolac: 30 ± 9; Diclofenac: 33 ± 11. Gender (M:F): 35/25. Ethnicity: NA
Further population details	1. Age: <60 years (ketorolac: 30 ± 9; Diclofenac: 33 ± 11). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I - II). 3. Type of surgery: Not applicable (Maxillofacial surgery). 4. Ketorolac variable dose; Diclofenac variable dose.
Indirectness of population	--
Interventions	(n=30) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. After induction of anesthesia, before surgical incision, the patients received IV Ketorolac Tromethamine 0.4mg/kg in 100ml 0.9% sodium chloride. The same IV dose was given three times at six hour intervals. Duration 24 hours . Concurrent medication/care: Oxycodone 0.03mg/kg (four hour maximum dose 0.4mg/kg and lock out period of 5 minutes was administered via PCA. Indirectness: No indirectness (n=30) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. After induction of anesthesia, before surgical incision, the patients received IV Diclofenac sodium 1mg/kg in 100ml 0.9% sodium chloride. This group received a placebo after 6 hours, the same diclofenac dose after a further 6 hours and a placebo following those 6 hours . Duration 24 hours. Concurrent medication/care: Oxycodone 0.03mg/kg (four hour

	maximum dose 0.4mg/kg and lock out period of 5 minutes was administered via PCA. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Oxycodone Consumption at 6 hours postoperatively; Mean; ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Oxycodone Consumption at 24 hours postoperatively; Mean; ;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Nausea at postoperatively; Group 1: 11/30, Group 2: 8/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Vomiting at postoperatively; Group 1: 7/30, Group 2: 3/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pruritis at postoperatively; Group 1: 5/30, Group 2: 5/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Tarkkila 1999[1243]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)

Countries and setting	Conducted in Finland; Setting: Helsinki University Central Hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I–II patients, aged 16–50 yr, undergoing elective tonsillectomy, allocated randomly to one of four groups of equal size
Exclusion criteria	Patients with a history of allergic reactions to NSAID, bronchial asthma, gastrointestinal ulceration or bleeding disorders were excluded.
Recruitment/selection of patients	undergoing elective tonsillectomy
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 31 (8); Diclofenac: 30 (10). Gender (M:F): 16/24. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 31 (8); Diclofenac: 30 (10)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I - II). 3. Type of surgery: Not applicable (Tonsillectomy). 4. Ketorolac 30mg; Diclofenac 75mg.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. After induction of anesthesia before surgical incision patients received Ketorolac 30mg as an IV infusion. In the ketorolac group, the same i.v. dose was repeated twice at 6-h intervals.. Duration intraoperatively to POD1. Concurrent medication/care: Rescue analgesic medication consisting of oxycodone 0.05 mg kg–1 i.v. during the first 2 h after operation (in the recovery room) and thereafter 1.0 mg kg–1 i.m. (on the ward) was administered on patient request. . Indirectness: No indirectness (n=20) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. After induction of anesthesia before surgical incision patients received Diclofenac 75mg as an IV infusion. In the diclofenac group, patients received placebo (saline) after 6 h and active drug (the initial dose) after 12 h.. Duration intraoperatively to POD1. Concurrent medication/care: Rescue analgesic medication consisting of oxycodone 0.05 mg kg–1 i.v. during the first 2 h after operation (in the recovery room) and thereafter 1.0 mg kg–1 i.m. (on the ward) was administered on patient request. . Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Nausea at postoperatively; Group 1: 9/19, Group 2: 11/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: postoperative bleeding ; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 5/19, Group 2: 5/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: postoperative bleeding ; Group 2 Number missing: 0 - Actual outcome: Itching at postoperatively; Group 1: 1/19, Group 2: 4/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: postoperative bleeding ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Uribe 2018[1292]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=53)
Countries and setting	Conducted in USA; Setting: Department of Anesthesiology, The Ohio State University Wexner Medical Center, United States
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Subjects scheduled to undergo arthroscopic knee surgery under general anesthesia who were 18 years and older, provided a written informed consent and self-reported their pain level by use of a paper Visual Analog Scale
Exclusion criteria	Subjects with inadequate IV access, a history of allergy or hypersensitivity to any component of ibuprofen or other NSAIDs, aspirin (or aspirin related products), opioids or COX-2 inhibitors, or had used analgesics <8 h prior to surgery were excluded from the study. Subjects with active significant anemia, history of asthma or heart failure, and recent history of chronicNSAIDs or opioid usewere also excluded fromthe study. Women who were pregnant were not enrolled in the study, and epidural anesthesia and nerve blocks were prohibited.
Recruitment/selection of patients	scheduled to undergo arthroscopic knee surgery under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Ibuprofen: 42.32 ± 12.37; Ketorolac: 44.6 ± 13.03. Gender (M:F): 35/. Ethnicity: NA
Further population details	1. Age: <60 years (Ibuprofen: 42.32 ± 12.37; Ketorolac: 44.6 ± 13.03). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (arthroscopic knee surgery). 4. Ibuprofen 1600mg; Ketorolac 30mg.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Non-steroidal anti-inflammatory - Ibuprofen. two doses of 800mg IV ibuprofen. Subjects in the ibuprofen group received 800mg of IV ibuprofen within 2h prior to surgery and a repeated second dose 4h after the initial dose if they had not been discharged. . Duration preoperative & postoperative. Concurrent medication/care: PACU rescue analgesic was managed with IV hydromorphone 0.5mg as needed. Subjects were discharged with a prescription of 800mg oral ibuprofen, every 6 h as needed and oxycodone/acetaminophen (5/325mg) every 4 h as needed. Indirectness: No indirectness (n=31) Intervention 2: Non-steroidal anti-inflammatory - Ketorolac. a single dose of 30mg ketorolac (15mg for subjects >65 years of age). The ketorolac group received matching placebo at hour 0 and 4 and 30mg of IVketorolac at the end of surgery.. Duration intraoperatively and postoperatively . Concurrent medication/care: vPACU rescue analgesic was managed with IV hydromorphone 0.5mg as needed. Subjects were discharged with a prescription of 800mg oral ibuprofen, every 6 h as needed and oxycodone/acetaminophen (5/325mg) every 4 h as needed. Indirectness: No indirectness
Funding	Study funded by industry (study was sponsored by Cumberland Pharmaceuticals, Inc)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus KETOROLAC	

Protocol outcome 1: Amount of additional medication use (< 6 hours post op) - Actual outcome: mean amounts of narcotic consumption (oral morphine conversion) at Pre PACU discharge; Group 1: mean 5.53 Milligrams (SD 5.89); n=20, Group 2: mean 19.92 Milligrams (SD 15.63); n=31; Comments: p value <0.001 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission
Study	**Walton 1993[1326]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Intervention + follow up: Interventions given as an injection when the patient is still under anesthetic, post tooth extraction, and then carried on for 3 days.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Adults aged 16-65 years having surgery for the extraction of impacted lower third molars, possibly involving bone removal under general anaesthetic.
Exclusion criteria	Study states; standard inclusion and exclusion criteria were used to recruit patients.
Age, gender and ethnicity	Age - Mean (range): Adults aged 16-65 years. . Gender (M:F): K group: 39/62, D group: 13/37, P group: 20/30. Ethnicity: NA Not stated
Further population details	1. Age: Systematic review: mixed 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Type of surgery: (Oral; molar extraction). 4. Ketorolac 30mg; Diclofenac 75mg.
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: Non-steroidal anti-inflammatory - Ketorolac. Single intramuscular 3 ml injection of 30 mg in the lateral muscle of the thigh while still under anaesthesia. 4 hours after intramuscular dose the

	patients received an oral dose of the same medication at 10 mg tds, and 10 mg qds on day 2 and 3. . Duration 3 days. Concurrent medication/care: Paracetamol was allowed as rescue medication throughout the trial. . Indirectness: No indirectness (n=50) Intervention 2: Non-steroidal anti-inflammatory - Diclofenac. Single intramuscular 3 ml injection of 75 mg in the lateral muscle of the thigh while still under anaesthesia. 4 hours after intramuscular dose the patients received an oral dose of the same medication at 75 mg one dose plus placebo bd, and 50 mg tds plus placebo one dose on day 2 and 3. . Duration 3 days. Concurrent medication/care: Paracetamol was used as rescue medication throughout trial. . Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Syntex Pharmaceuticals Limited provided financial assistance and the statistical analysis of this study.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus DICLOFENAC Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain score (AUC) during intramuscular phase at up to 4 hours; Mean; , Comments: K group n=97, AUC= 60.0; D group n=50, AUC= 61.9; p=0.0029; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Adverse events (nausea, vomiting,dizziness, dark urine, drowsiness, unsettled stomach, hot and cold flush) at 3 days, during oral medication phase; Group 1: 11/101, Group 2: 0/50 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - no details on missing people although it is clear from other results tables that people were missing in the groups; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Wattchow 2009[1342]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	(n=210)
Countries and setting	Conducted in Australia; Setting: Flinders Medical Centre, Australia
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	undergo elective surgery that involved substantial handling of the intestines. Surgical procedures included laparotomy for colorectal procedures (resections, stoma formation or relocation, reversal of Hartman's procedure) and small bowel resections.
Exclusion criteria	Exclusion criteria were: a calculated (Cockcroft⁄Gault formula) creatinine clearance less than 30 mL⁄min; allergy to NSAIDs, recent gastrointestinal ulcers; asthma or therapeutic anticoagulation.
Recruitment/selection of patients	undergo elective surgery that involved substantial handling of the intestines. Surgical procedures included laparotomy for colorectal procedures (resections, stoma formation or relocation, reversal of Hartman's procedure) and small bowel resections.
Age, gender and ethnicity	Age - Mean (SD): Diclofenac: 59 ± 14; Celecoxib: 65 ± 14. Gender (M:F): 78/65. Ethnicity: NA
Further population details	1. Age: <60 years (Diclofenac: 59 ± 14; Celecoxib: 65 ± 14). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (surgery that involved substantial handling of the intestines). 4. Diclofenac 50mg; Celecoxib 100mg.
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: Non-steroidal anti-inflammatory - Diclofenac. diclofenac (50 mg) commencing one to 2 h prior to surgery. For morning surgery, a second dose was given at 2000; if afternoon, the next dose was 08:00 h the following day. Dosing stopped 7 days after surgery or at discharge (if earlier). . Duration up to 7 days postoperatively. Concurrent medication/care: Pain relief was with patient controlled analgesia (PCA) or epidural infusions (high lumbar, routine thoracic epidurals were not used by the anaesthetic department); the method was determined by the anaesthetic staff. PCA was given as a bolus injection with morphine 1 mg⁄mL (5 min lockout intervals). Fentanyl (10 or 20 lg⁄mL) was used for patients who could not tolerate morphine. Epidurals were infused with Ropivicaine (0.2%) and Fentanyl (2 or 4 lg⁄mL) at 2 to 6mL⁄h. The concentration, rate, bolus dosing and cessation were determined by the nursing and anesthetic staff. Upon cessation, pain was managed with oral paracetamol or oxycodone (NSAIDs were excluded). . Indirectness: No indirectness

	(n=74) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. celecoxib (100 mg) commencing one to 2 h prior to surgery. For morning surgery, a second dose was given at 2000; if afternoon, the next dose was 08:00 h the following day. Dosing stopped 7 days after surgery or at discharge (if earlier).. Duration up to 7 days postoperatively. Concurrent medication/care: Pain relief was with patient controlled analgesia (PCA) or epidural infusions (high lumbar, routine thoracic epidurals were not used by the anaesthetic department); the method was determined by the anaesthetic staff. PCA was given as a bolus injection with morphine 1 mg⁄mL (5 min lockout intervals). Fentanyl (10 or 20 lg⁄mL) was used for patients who could not tolerate morphine. Epidurals were infused with Ropivicaine (0.2%) and Fentanyl (2 or 4 lg⁄mL) at 2 to 6mL⁄h. The concentration, rate, bolus dosing and cessation were determined by the nursing and anesthetic staff. Upon cessation, pain was managed with oral paracetamol or oxycodone (NSAIDs were excluded). . Indirectness: No indirectness
Funding	No funding (study was conducted entirely within the clinical resources of the Flinders Medical Centre)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus CELECOXIB Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain scores at day 0 postoperatively ; median (IQR): Diclofenac: 3.5 (1-5); Celecoxib: 4 (2-6) visual analogue scale 0-10 Top=High is poor outcome; Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) - Actual outcome: Vomiting at postoperatively; Group 1: 20/69, Group 2: 16/74 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: length of stay at postoperatively; Median (IQR): Diclofenac: 7 (5-9); Celecoxib: 7 (5-10) days); Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ;

study	Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Hospital readmission

Study	**White 2011[1354]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=180)
Countries and setting	Conducted in USA; Setting: Tertiary medical centre, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients scheduled for superficial (noncavitary) surgical procedures (e.g., hernia repair, partial mastectomy, or joint arthroscopy)
Exclusion criteria	Patients were excluded if they had difficulty understanding English, had an allergy or contraindication to taking NSAIDs, chronically used NSAIDs, had received an opioid analgesic medication within a 12-hour period before the operation, were pregnant or breast-feeding, had a history of alcohol or drug abuse, had a bleeding disorder, or had clinically significant neurologic, cardiovascular, renal, hepatic, or gastrointestinal diseases.
Recruitment/selection of patients	patients scheduled for superficial (noncavitary) surgical procedures (e.g., hernia repair, partial mastectomy, or joint arthroscopy)
Age, gender and ethnicity	Age - Mean (SD): Ibuprofen: 50 ± 13; Celecoxib: 48 ± 13. Gender (M:F): 74/46. Ethnicity: NA
Further population details	1. Age: <60 years (Ibuprofen: 50 ± 13; Celecoxib: 48 ± 13). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 54; ASA II: 54; ASA III: 14). 3. Type of surgery: Not applicable (superficial (noncavitary) surgical procedures). 4. Ibuprofen 400mg; Celecoxib 400mg.
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Non-steroidal anti-inflammatory - Ibuprofen. Group 3 (ibuprofen) received ibuprofen 400 mg (1 tablet) orally in the recovery room and 400 mg orally at bedtime on the day of surgery, followed by 400 mg orally 3 times a day for 3 days after surgery. . Duration day or surgery to 3 days postoperatively. Concurrent

	medication/care: Patients complaining of moderate-to-severe pain (VRS score≥4) were treated with hydromorphone, 0.1 to 0.2 mg IV.. Indirectness: No indirectness (n=60) Intervention 2: Non-steroidal anti-inflammatory - COX2 inhibitor. Group 2 (celecoxib) received celecoxib 400 mg (2 capsules) orally in the recovery room and 1 placebo capsule at bedtime on the day of surgery, followed by celecoxib 200 mg twice a day 3 days after surgery. Duration day or surgery to 3 days postoperatively. Concurrent medication/care: Patients complaining of moderate-to-severe pain (VRS score≥4) were treated with hydromorphone, 0.1 to 0.2 mg IV.. Indirectness: No indirectness
Funding	Other (Cedars Sinai Medical Center in Los Angeles received an educational grant from Wyeth for this investigator-initiated study)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus CELECOXIB

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Postoperative pain score at 1h postoperatively; Group 1: mean 2 (SD 2); n=60, Group 2: mean 2 (SD 2); n=60; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Postoperative pain score at 24h postoperatively; Group 1: mean 5 (SD 3); n=60, Group 2: mean 5 (SD 3); n=60; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Nausea at pre-discharge; Group 1: 4/60, Group 2: 2/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Vomiting at pre-discharge; Group 1: 0/60, Group 2: 1/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Headache at pre-discharge; Group 1: 0/60, Group 2: 3/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 4: Functional measures (including time to mobilisation) - Actual outcome: Time to ambulation at Postoperatively; Group 1: mean 88 minutes (SD 28); n=60, Group 2: mean 92 minutes (SD 28); n=60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Wong 2010[1362]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=66)
Countries and setting	Conducted in Taiwan; Setting: St. Martin De Porres Hospital, Chia-yi, Taiwan
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	20 and 40 years of age, of ASA physical status I or II, weighing 60e90 kg, and standing 155-170 cm.
Exclusion criteria	The parturients were free of specific cardiovascular, neurological, hematological or gastrointestinal diseases, and were scheduled for elective cesarean section at term under spinal anesthesia.
Recruitment/selection of patients	elective cesarean section at term under spinal anesthesia
Age, gender and ethnicity	Age - Mean (SD): Ketorolac: 30.7 ± 4.4; Parecoxib: 30.8 ± 5.6. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Ketorolac: 30.7 ± 4.4; Parecoxib: 30.8 ± 5.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: gynae-oncology (elective cesarean section). 4. Parecoxib 40mg; Ketorolac 30mg.
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Non-steroidal anti-inflammatory - COX2 inhibitor. When the parturients were transferred to Post-Anesthesia Recovery Room Group P patients received an intravenous bolus of 40 mg parecoxib as a loading dose post-operatively; then two subsequent bolus doses of 20 mg parecoxib were

	separately given at 24-h and 48-h intervals, after the initial dose.. Duration 3 days post-delivery . Concurrent medication/care: morphine in continuing dose of 0.2 mg/h, and the bolus dose of 2 mg (each bag of basic PCA solution contained morphine 50 mg in normal saline 250 mL).. Indirectness: No indirectness (n=33) Intervention 2: Non-steroidal anti-inflammatory - Ketorolac. Group K patients received a loading intravenous bolus of 30 mg ketorolac, then 90 mg ketorolac combined with morphine in a PCA fashion throughout the study course.. Duration 3 days post delivery. Concurrent medication/care: morphine in continuing dose of 0.2 mg/h, and the bolus dose of 2 mg (each bag of basic PCA solution contained morphine 50 mg in normal saline 250 mL).. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Pfizer Limited for providing the drug (Parecoxib).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOROLAC versus PARECOXIB

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain score at postoperative; Median (range): Ketorolac: 4.3 (0-8); Parecoxib: 3.1 (0-5), Comments: p value 0.005);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
- Actual outcome: Nausea and vomiting at 24 postoperative; Group 1: 2/33, Group 2: 4/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Length of hospital stay
- Actual outcome: Hospital stay at postoperative; Group 1: mean 6 days (SD 0.6); n=33, Group 2: mean 6 days (SD 0.7); n=33; Comments: p value 0.348
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

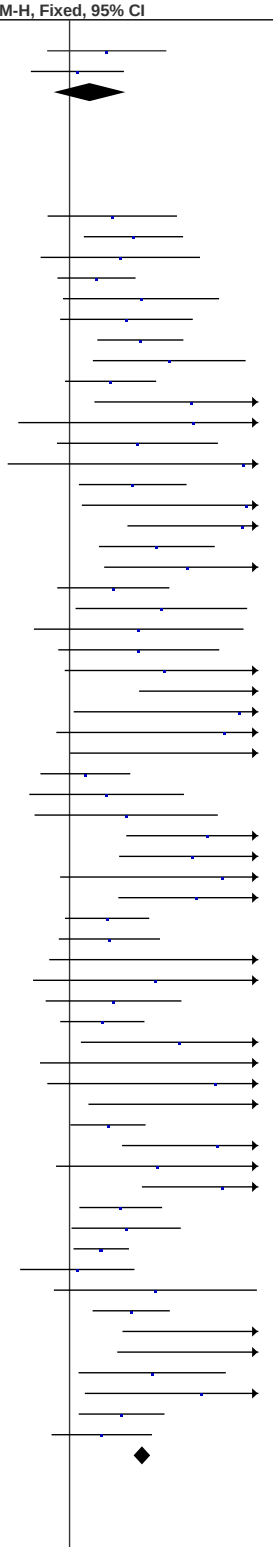
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures (including time to mobilisation) ; Length of stay in intensive care unit ; Hospital readmission

Appendix D: Forest plots

D.1 NSAIDs versus placebo

Figure 26: Participants with at least 50% pain relief over 6 hours

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Aspirin 500 mg versus placebo						
Nelson 1994a	20	65	8	41	0.4%	1.58 [0.77, 3.24]
Seymour 1992	25	70	12	37	0.7%	1.10 [0.63, 1.93]
Subtotal (95% CI)		**135**		**78**	**1.2%**	**1.28 [0.82, 2.00]**
Total events	45		20			
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
1.1.2 Aspirin 600 or 650 mg versus placebo						
Bloomfield 1967	9	16	6	18	0.3%	1.69 [0.77, 3.69]
Boraks 1987	23	41	10	39	0.5%	2.19 [1.20, 3.98]
Breivik 1984	9	29	5	30	0.2%	1.86 [0.71, 4.90]
Calimlim 1977	16	23	13	26	0.6%	1.39 [0.87, 2.23]
Clark 1989	12	40	5	40	0.2%	2.40 [0.93, 6.19]
Cooper 1977	13	37	7	40	0.3%	2.01 [0.90, 4.48]
Cooper 1979a	27	47	14	58	0.6%	2.38 [1.42, 4.00]
Cooper 1982	14	38	5	46	0.2%	3.39 [1.34, 8.56]
Cooper 1983	21	43	13	44	0.6%	1.65 [0.95, 2.86]
Cooper 1986	13	40	3	41	0.1%	4.44 [1.37, 14.42]
Cooper 1988	4	29	1	33	0.0%	4.55 [0.54, 38.45]
Cooper 1991	11	46	5	48	0.2%	2.30 [0.86, 6.10]
Cooper 1992	4	28	0	26	0.0%	8.38 [0.47, 148.43]
Coutinho 1976	13	15	6	15	0.3%	2.17 [1.13, 4.15]
De Vroey 1977	9	32	1	31	0.0%	8.72 [1.17, 64.82]
Desjardins 1984	17	40	2	39	0.1%	8.29 [2.05, 33.51]
Fliedner 1984	25	83	9	87	0.4%	2.91 [1.45, 5.86]
Forbes 1980	15	38	4	43	0.2%	4.24 [1.54, 11.68]
Forbes 1982	17	42	9	38	0.4%	1.71 [0.87, 3.37]
Forbes 1983	12	39	4	40	0.2%	3.08 [1.09, 8.72]
Forbes 1984	6	24	3	28	0.1%	2.33 [0.65, 8.34]
Forbes 1986	10	36	5	42	0.2%	2.33 [0.88, 6.20]
Forbes 1989	9	31	3	33	0.1%	3.19 [0.95, 10.72]
Forbes 1990a	17	68	0	75	0.0%	38.55 [2.36, 629.01]
Forbes 1990b	8	32	1	32	0.0%	8.00 [1.06, 60.32]
Forbes 1991	7	41	1	39	0.0%	6.66 [0.86, 51.67]
Forbes 1992	8	38	0	38	0.0%	17.00 [1.02, 284.47]
Frame 1986	14	25	12	26	0.5%	1.21 [0.71, 2.08]
Gaston 1984	9	40	6	42	0.3%	1.57 [0.62, 4.02]
Gaston 1986	8	38	4	38	0.2%	2.00 [0.66, 6.09]
Herbertson 1994	23	50	4	47	0.2%	5.41 [2.02, 14.46]
Holland 1988	18	20	4	20	0.2%	4.50 [1.85, 10.94]
Honig 1978	9	25	1	18	0.1%	6.48 [0.90, 46.71]
Jain 1985a	19	30	4	30	0.2%	4.75 [1.83, 12.31]
Jain 1985a	19	29	12	29	0.5%	1.58 [0.95, 2.63]
Jain 1986a	17	37	11	39	0.5%	1.63 [0.88, 3.00]
Jain 1986b	6	45	0	47	0.0%	13.57 [0.79, 234.01]
Kempf 1987	6	24	2	23	0.1%	2.88 [0.64, 12.82]
London 1983a	12	40	7	40	0.3%	1.71 [0.75, 3.90]
London 1983b	22	41	14	39	0.6%	1.49 [0.90, 2.48]
Mardirossian 1985	11	40	3	42	0.1%	3.85 [1.16, 12.79]
Markowitz 1985	5	47	0	53	0.0%	12.38 [0.70, 218.00]
McQuay 1987	6	30	1	30	0.0%	6.00 [0.77, 46.87]
Mehlisch 1984	9	49	0	55	0.0%	21.28 [1.27, 356.34]
Mehlisch 1990	25	40	16	41	0.7%	1.60 [1.02, 2.52]
Mehlisch 1994	18	51	3	52	0.1%	6.12 [1.92, 19.51]
Nelson 1985	9	40	3	39	0.1%	2.92 [0.85, 10.01]
Nelson 1994b	26	50	4	50	0.2%	6.50 [2.45, 17.27]
Olsen 1997	27	50	15	52	0.7%	1.87 [1.14, 3.08]
Or 1988	16	27	8	27	0.4%	2.00 [1.03, 3.87]
Parkhouse 1969	85	169	29	85	1.7%	1.47 [1.06, 2.05]
Patel 1991	11	30	10	30	0.5%	1.10 [0.55, 2.19]
Rowe 1985	9	43	3	41	0.1%	2.86 [0.83, 9.83]
Sunshine 1983a	27	30	11	26	0.5%	2.13 [1.34, 3.38]
Sunshine 1983b	14	29	0	31	0.0%	30.93 [1.93, 496.05]
Sunshine 1983c	14	30	0	30	0.0%	29.00 [1.81, 465.07]
Sunshine 1988	11	15	4	15	0.2%	2.75 [1.13, 6.72]
Wang 1982	10	25	2	25	0.1%	5.00 [1.22, 20.55]
Winter 1983a	24	37	12	35	0.6%	1.89 [1.13, 3.17]
Winter 1983b	17	42	12	44	0.5%	1.48 [0.81, 2.72]
Subtotal (95% CI)		**2334**		**2310**	**16.3%**	**2.46 [2.22, 2.72]**
Total events	905		352			
Heterogeneity: Chi² = 93.51, df = 59 (P = 0.003); I² = 37%						
Test for overall effect: Z = 17.04 (P < 0.00001)						



1.1.3 Aspirin 900 or 1000 mg versus placebo

Forbes 1990a	17	71	0	75	0.0%	36.94 [2.26, 603.05]
Herrmann 1980a	32	50	16	50	0.7%	2.00 [1.27, 3.15]
Herrmann 1980b	19	40	4	42	0.2%	4.99 [1.86, 13.39]
Lehnert 1990	20	45	5	42	0.2%	3.73 [1.54, 9.05]
Seymour 1992	25	75	12	37	0.7%	1.03 [0.58, 1.81]
Seymour 2003	25	59	3	32	0.2%	4.52 [1.48, 13.82]
Subtotal (95% CI)		**340**		**278**	**2.1%**	**2.70 [2.00, 3.64]**
Total events	138		40			

Heterogeneity: Chi² = 19.09, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 6.53 (P < 0.00001)

1.1.4 Aspirin 1200 mg versus placebo

Holland 1988	28	40	9	40	0.4%	3.11 [1.69, 5.73]
London 1983b	25	40	14	39	0.6%	1.74 [1.07, 2.82]
Seymour 1986	32	60	2	30	0.1%	8.00 [2.05, 31.16]
Subtotal (95% CI)		**140**		**109**	**1.2%**	**2.86 [1.95, 4.20]**
Total events	85		25			

Heterogeneity: Chi² = 6.34, df = 2 (P = 0.04); I² = 68%
Test for overall effect: Z = 5.38 (P < 0.00001)

1.1.5 Diclofenac fast-acting 25 mg versus placebo

Riff 2009	21	102	3	99	0.1%	6.79 [2.09, 22.06]
Zuniga 2010	15	63	1	61	0.0%	14.52 [1.98, 106.61]
Subtotal (95% CI)		**165**		**160**	**0.2%**	**8.73 [3.18, 23.97]**
Total events	36		4			

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 4.20 (P < 0.0001)

1.1.6 Diclofenac fast-acting 50 mg versus placebo

Ahlstrom 1993	21	35	3	50	0.1%	10.00 [3.23, 30.96]
Bakshi 1994	62	83	31	82	1.4%	1.98 [1.46, 2.68]
Hofele 2006	55	74	11	39	0.6%	2.64 [1.57, 4.42]
Zuniga 2010	18	62	1	61	0.0%	17.71 [2.44, 128.58]
Subtotal (95% CI)		**254**		**232**	**2.2%**	**2.90 [2.23, 3.76]**
Total events	156		46			

Heterogeneity: Chi² = 14.01, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 8.00 (P < 0.00001)

1.1.7 Diclofenac fast-acting 100 mg versus placebo

Zuniga 2004	16	29	0	15	0.0%	17.60 [1.13, 274.56]
Zuniga 2010	19	63	1	61	0.0%	18.40 [2.54, 133.22]
Subtotal (95% CI)		**92**		**76**	**0.1%**	**18.09 [3.60, 90.75]**
Total events	35		1			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.52 (P = 0.0004)

1.1.8 Diclofenac potassium 25 mg versus placebo

Hersh 2004	43	63	11	68	0.5%	4.22 [2.39, 7.44]
Kubitzek 2003	42	83	7	84	0.3%	6.07 [2.90, 12.73]
Nelson 1994	23	50	4	50	0.2%	5.75 [2.14, 15.42]
Olson 1997	32	52	15	52	0.7%	2.13 [1.32, 3.44]
Subtotal (95% CI)		**248**		**254**	**1.6%**	**3.88 [2.84, 5.32]**
Total events	140		37			

Heterogeneity: Chi² = 8.13, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 8.46 (P < 0.00001)

1.1.9 Diclofenac potassium 50 mg versus placebo

Bakshi 1992	35	51	10	46	0.5%	3.16 [1.77, 5.63]
Herbertson 1995	29	52	5	52	0.2%	5.80 [2.44, 13.81]
Hersh 2004	44	68	11	68	0.5%	4.00 [2.26, 7.06]
Hofele 2006	55	74	11	39	0.6%	2.64 [1.57, 4.42]
Mehlisch 1995	28	53	4	52	0.2%	6.87 [2.59, 18.21]
Nelson 1994	28	50	4	50	0.2%	7.00 [2.65, 18.49]
Olson 1997	34	50	15	52	0.7%	2.36 [1.48, 3.76]
Subtotal (95% CI)		**398**		**359**	**2.9%**	**3.68 [2.90, 4.68]**
Total events	253		60			

Heterogeneity: Chi² = 9.76, df = 6 (P = 0.14); I² = 39%
Test for overall effect: Z = 10.69 (P < 0.00001)

1.1.10 Diclofenac potassium 100 mg versus placebo

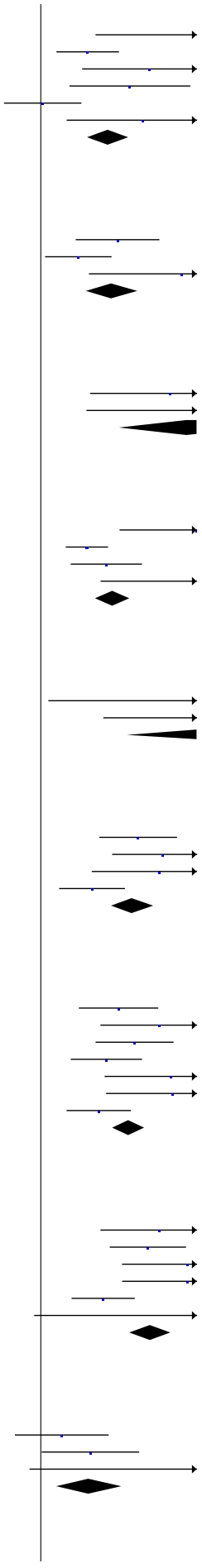
Herbertson 1995	29	52	5	52	0.2%	5.80 [2.44, 13.81]
Hersh 2004	52	66	11	68	0.5%	4.87 [2.80, 8.49]
Mehlisch 1995	35	52	4	52	0.2%	8.75 [3.35, 22.86]
Nelson 1994	35	50	4	50	0.2%	8.75 [3.36, 22.79]
Olson 1997	37	51	15	52	0.7%	2.52 [1.59, 3.98]
Zuniga 2004	13	29	0	15	0.0%	14.40 [0.91, 226.77]
Subtotal (95% CI)		**300**		**289**	**1.8%**	**5.05 [3.74, 6.82]**
Total events	201		39			

Heterogeneity: Chi² = 12.04, df = 5 (P = 0.03); I² = 58%
Test for overall effect: Z = 10.55 (P < 0.00001)

1.1.11 Diclofenac sodium 50 mg versus placebo

Bakshi 1992	16	54	10	46	0.5%	1.36 [0.69, 2.70]
Chang 2002	32	121	8	63	0.5%	2.08 [1.02, 4.25]
Cooper 1996	10	18	0	11	0.0%	13.26 [0.85, 206.11]
Subtotal (95% CI)		**193**		**120**	**1.0%**	**2.04 [1.26, 3.31]**
Total events	58		18			

Heterogeneity: Chi² = 3.12, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 2.89 (P = 0.004)



1.1.12 Diclofenac sodium 100 mg versus placebo

Desjardins 2004	13	85	4	82	0.2%	3.14 [1.07, 9.22]
Subtotal (95% CI)		**85**		**82**	**0.2%**	**3.14 [1.07, 9.22]**
Total events	13		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.08 (P = 0.04)

1.1.13 Diflunisal 250mg versus placebo

De Vroey 1978	13	30	6	31	0.3%	2.24 [0.98, 5.12]
Forbes 1982a	25	39	9	38	0.4%	2.71 [1.46, 5.02]
Honig 1978a	8	29	1	28	0.0%	7.72 [1.03, 57.82]
Subtotal (95% CI)		**98**		**97**	**0.7%**	**2.85 [1.76, 4.63]**
Total events	46		16			

Heterogeneity: Chi² = 1.30, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 4.25 (P < 0.0001)

1.1.14 Diflunisal 500mg versus placebo

De Vroey 1978	20	30	6	31	0.3%	3.44 [1.61, 7.38]
Forbes 1982a	21	41	9	38	0.4%	2.16 [1.14, 4.12]
Forbes 1982b	19	32	6	30	0.3%	2.97 [1.37, 6.42]
Forbes 1983a	11	26	1	26	0.0%	11.00 [1.53, 79.16]
Forbes 1983b	22	39	4	40	0.2%	5.64 [2.14, 14.88]
Honig 1978a	11	30	1	28	0.0%	10.27 [1.42, 74.45]
Subtotal (95% CI)		**198**		**193**	**1.2%**	**3.75 [2.59, 5.42]**
Total events	104		27			

Heterogeneity: Chi² = 6.02, df = 5 (P = 0.30); I² = 17%
Test for overall effect: Z = 7.02 (P < 0.00001)

1.1.15 Diflunisal 1000mg versus placebo

Forbes 1982a	26	41	9	38	0.4%	2.68 [1.45, 4.96]
Forbes 1982b	20	32	6	30	0.3%	3.13 [1.46, 6.71]
Forbes 1983a	13	28	1	26	0.0%	12.07 [1.70, 85.93]
Forbes 1983b	28	40	4	40	0.2%	7.00 [2.70, 18.13]
Lindenmuth 1989	25	41	6	41	0.3%	4.17 [1.91, 9.08]
Subtotal (95% CI)		**182**		**175**	**1.2%**	**4.14 [2.85, 5.99]**
Total events	112		26			

Heterogeneity: Chi² = 4.75, df = 4 (P = 0.31); I² = 16%
Test for overall effect: Z = 7.51 (P < 0.00001)

1.1.16 Etodolac 50 mg versus placebo

Fliedner 1984	10	37	14	87	0.4%	1.68 [0.82, 3.43]
Gaston 1984	11	39	6	42	0.3%	1.97 [0.81, 4.83]
Gaston 1986	10	37	6	38	0.3%	1.71 [0.69, 4.23]
Nelson 1985	13	41	8	39	0.4%	1.55 [0.72, 3.32]
Subtotal (95% CI)		**154**		**206**	**1.3%**	**1.71 [1.14, 2.56]**
Total events	44		34			

Heterogeneity: Chi² = 0.17, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)

1.1.17 Etodolac 100 mg versus placebo

Fliedner 1984	36	87	14	87	0.6%	2.57 [1.50, 4.42]
Friedrich 1983	23	40	16	40	0.7%	1.44 [0.90, 2.29]
Gaston 1986	15	38	6	38	0.3%	2.50 [1.09, 5.75]
Hutton 1983	15	44	6	43	0.3%	2.44 [1.05, 5.71]
Nelson 1985	14	42	8	39	0.4%	1.63 [0.77, 3.44]
Subtotal (95% CI)		**251**		**247**	**2.3%**	**2.03 [1.53, 2.70]**
Total events	103		50			

Heterogeneity: Chi² = 3.62, df = 4 (P = 0.46); I² = 0%
Test for overall effect: Z = 4.88 (P < 0.00001)

1.1.18 Etodolac 200 mg versus placebo

Fliedner 1984	42	86	14	87	0.6%	3.03 [1.79, 5.14]
Gaston 1984	13	40	6	42	0.3%	2.27 [0.96, 5.40]
Gaston 1986	18	38	6	38	0.3%	3.00 [1.34, 6.72]
Giglio 1986	16	42	2	41	0.1%	7.81 [1.92, 31.85]
Hersh 1999	17	47	2	47	0.1%	8.50 [2.08, 34.76]
Hutton 1983	17	41	6	43	0.3%	2.97 [1.30, 6.79]
Nelson 1985	22	39	8	39	0.4%	2.75 [1.40, 5.41]
Subtotal (95% CI)		**333**		**337**	**2.0%**	**3.34 [2.47, 4.51]**
Total events	145		44			

Heterogeneity: Chi² = 4.44, df = 6 (P = 0.62); I² = 0%
Test for overall effect: Z = 7.88 (P < 0.00001)

1.1.19 Etodolac 400 mg versus placebo

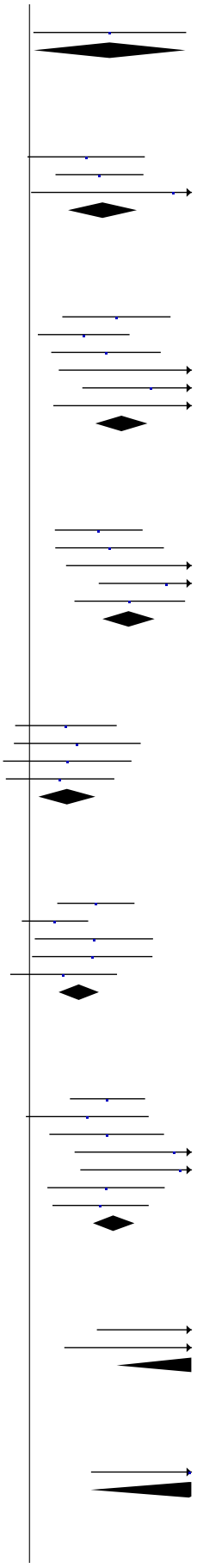
Giglio 1986	20	39	2	41	0.1%	10.51 [2.63, 42.03]
Hersh 1999	23	46	1	23	0.1%	11.50 [1.66, 79.91]
Subtotal (95% CI)		**85**		**64**	**0.1%**	**10.91 [3.48, 34.21]**
Total events	43		3			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 4.10 (P < 0.0001)

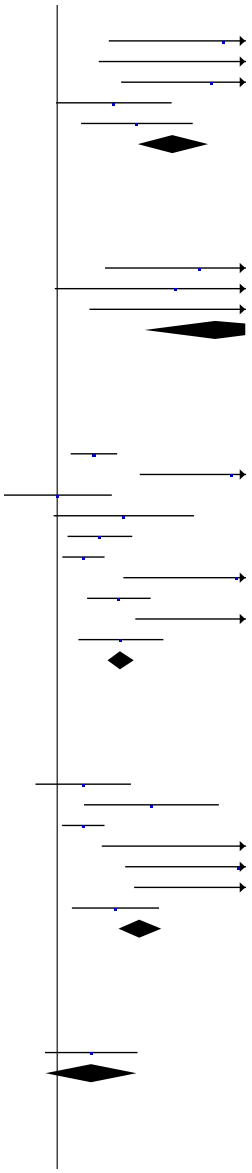
1.1.20 Etodolac 1200 mg ER versus placebo

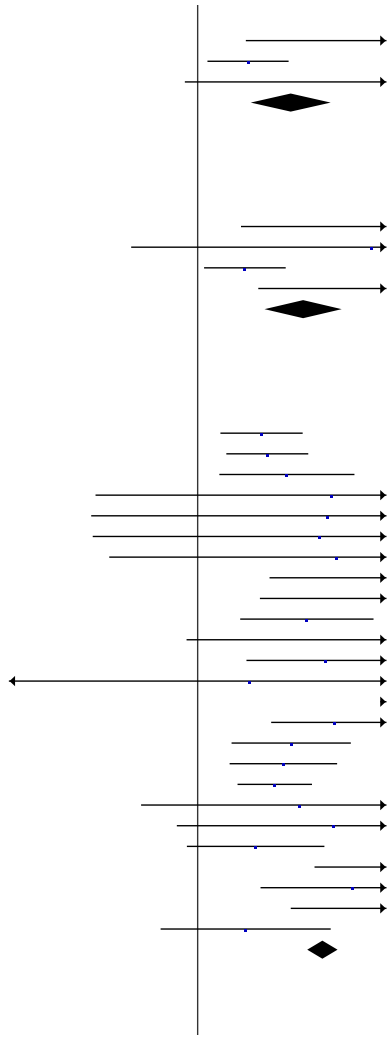
Hersh 1999	20	48	2	47	0.1%	9.79 [2.42, 39.58]
Subtotal (95% CI)		**48**		**47**	**0.1%**	**9.79 [2.42, 39.58]**
Total events	20		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.20 (P = 0.001)



1.1.21 Fenoprofen 200 mg versus placebo						
Cooper 1984	17	39	2	35	0.1%	7.63 [1.90, 30.70]
Davie 1982	13	30	0	30	0.0%	27.00 [1.68, 434.53]
Laska 1981 (1)	19	26	3	27	0.1%	6.58 [2.21, 19.60]
Laska 1981 (2)	14	23	7	23	0.3%	2.00 [0.99, 4.03]
Laska 1981 (3)	20	28	7	26	0.3%	2.65 [1.35, 5.21]
Subtotal (95% CI)		**146**		**141**	**0.9%**	**4.15 [2.71, 6.36]**
Total events	83		19			
Heterogeneity: Chi² = 9.03, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 6.53 (P < 0.00001)						
1.1.22 Flurbiprofen 25 mg versus placebo						
Cooper 1986	16	39	3	42	0.1%	5.74 [1.81, 18.20]
Forbes 1989b	8	31	2	33	0.1%	4.26 [0.98, 18.52]
Sunshine 1983	12	32	0	31	0.0%	24.24 [1.50, 392.55]
Subtotal (95% CI)		**102**		**106**	**0.2%**	**6.96 [2.95, 16.47]**
Total events	36		5			
Heterogeneity: Chi² = 1.31, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
1.1.23 Flurbiprofen 50 mg versus placebo						
Boraks 1987	37	40	23	39	1.1%	1.57 [1.19, 2.07]
Cooper 1986	26	43	3	42	0.1%	8.47 [2.77, 25.86]
Cooper 1988	11	30	12	33	0.5%	1.01 [0.53, 1.94]
Cooper 1991	19	42	5	25	0.3%	2.26 [0.97, 5.30]
De Lia 1986	27	32	15	30	0.7%	1.69 [1.15, 2.49]
Dionne 1994	26	26	18	25	0.8%	1.38 [1.07, 1.77]
Forbes 1989b	18	33	2	33	0.1%	9.00 [2.27, 35.73]
Morrison 1986	38	47	19	50	0.8%	2.13 [1.45, 3.11]
Sunshine 1983	19	29	0	31	0.0%	41.60 [2.63, 658.97]
Sunshine 1986	24	31	11	31	0.5%	2.18 [1.31, 3.64]
Subtotal (95% CI)		**353**		**339**	**5.0%**	**2.19 [1.86, 2.57]**
Total events	245		108			
Heterogeneity: Chi² = 39.92, df = 9 (P < 0.00001); I² = 77%						
Test for overall effect: Z = 9.53 (P < 0.00001)						
1.1.24 Flurbiprofen 100 mg versus placebo						
Cooper 1988	15	30	12	33	0.5%	1.38 [0.77, 2.45]
Cooper 1991	26	41	5	25	0.3%	3.17 [1.40, 7.18]
Dionne 1994	22	22	18	25	0.8%	1.37 [1.07, 1.77]
Forbes 1989a	15	26	0	23	0.0%	27.56 [1.74, 436.23]
Forbes 1989b	20	36	2	33	0.1%	9.17 [2.32, 36.24]
Sunshine 1983	20	31	0	31	0.0%	41.00 [2.59, 649.28]
Sunshine 1986	21	29	11	31	0.5%	2.04 [1.21, 3.45]
Subtotal (95% CI)		**215**		**201**	**2.2%**	**2.77 [2.14, 3.59]**
Total events	139		48			
Heterogeneity: Chi² = 46.05, df = 6 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 7.70 (P < 0.00001)						
1.1.25 Flurbiprofen 150 mg versus placebo						
Cooper 1988	16	29	12	33	0.5%	1.52 [0.87, 2.65]
Subtotal (95% CI)		**29**		**33**	**0.5%**	**1.52 [0.87, 2.65]**
Total events	16		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						





1.1.26 Ibuprofen 50 mg versus placebo

Forbes 1991a	16	57	0	51	0.0%	29.59 [1.82, 480.96]
Schou 1998	27	51	16	56	0.7%	1.85 [1.14, 3.02]
Sunshine 1996	7	51	0	50	0.0%	14.71 [0.86, 250.93]
Subtotal (95% CI)		**159**		**157**	**0.7%**	**3.15 [1.94, 5.12]**
Total events	50		16			

Heterogeneity: Chi² = 8.15, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 4.63 (P < 0.00001)

1.1.27 Ibuprofen 100 mg versus placebo

Forbes 1991a	13	49	0	51	0.0%	28.08 [1.71, 459.85]
Jain 1986	3	39	0	47	0.0%	8.40 [0.45, 157.84]
Schou 1998	27	53	16	56	0.7%	1.78 [1.09, 2.91]
Sunshine 1996	17	51	0	50	0.0%	34.33 [2.12, 555.79]
Subtotal (95% CI)		**192**		**204**	**0.8%**	**3.68 [2.29, 5.92]**
Total events	60		16			

Heterogeneity: Chi² = 13.18, df = 3 (P = 0.004); I² = 77%
Test for overall effect: Z = 5.39 (P < 0.00001)

1.1.28 Ibuprofen 200 mg versus placebo

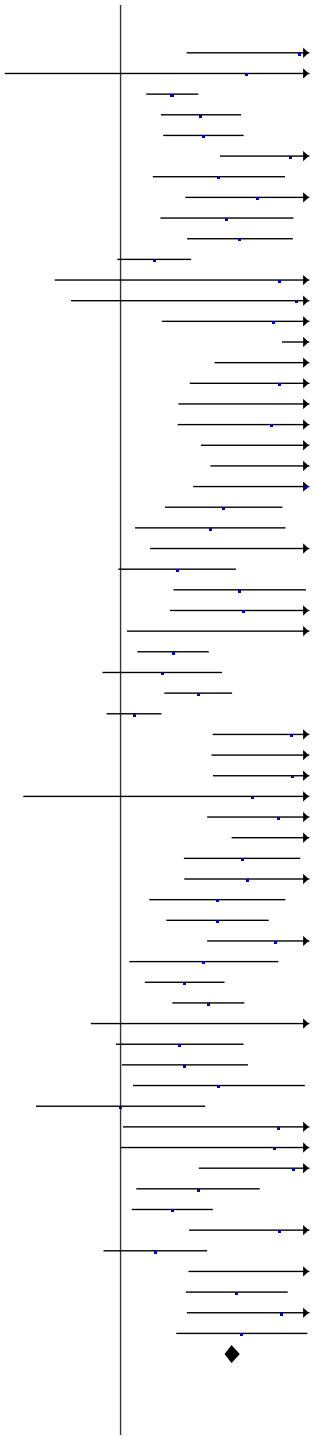
Black 2002	58	100	13	49	0.8%	2.19 [1.33, 3.59]
Black 2002 (4)	61	100	13	50	0.8%	2.35 [1.43, 3.84]
Cooper 1977	17	38	6	40	0.3%	2.98 [1.32, 6.76]
Cooper 1996a (5)	3	18	0	13	0.0%	5.16 [0.29, 92.04]
Cooper 1996a	3	19	0	13	0.0%	4.90 [0.27, 87.59]
Desjardins 2002	9	50	0	11	0.0%	4.47 [0.28, 71.59]
Desjardins 2002 (6)	10	49	0	12	0.0%	5.46 [0.34, 87.19]
Forbes 1991a	18	48	0	51	0.0%	39.27 [2.43, 634.05]
Hersch 1993a	17	51	0	51	0.0%	35.00 [2.16, 566.84]
Hersh 2000	43	61	5	27	0.3%	3.81 [1.70, 8.54]
Jain 1986	7	47	0	47	0.0%	15.00 [0.88, 255.36]
Kiersch 1993	37	81	4	42	0.2%	4.80 [1.83, 12.55]
McQuay 1996	2	31	0	11	0.0%	1.88 [0.10, 36.29]
Medve 2001	114	240	5	239	0.2%	22.70 [9.44, 54.60]
Mehlisch 2002 (7)	64	100	6	50	0.4%	5.33 [2.48, 11.46]
Mehlisch 2002	44	100	7	50	0.4%	3.14 [1.53, 6.47]
Nelson 1994	44	77	8	40	0.5%	2.86 [1.49, 5.47]
Schou 1998	36	49	16	56	0.7%	2.57 [1.64, 4.02]
Seymour 1996	7	18	1	9	0.1%	3.50 [0.50, 24.27]
Seymour 1996 (8)	9	17	1	10	0.1%	5.29 [0.78, 35.85]
Seymour 2000	14	59	7	60	0.3%	2.03 [0.88, 4.68]
Sunshine 1996	33	50	0	50	0.0%	67.00 [4.22, 1064.23]
Sunshine 1998	20	35	3	35	0.1%	6.67 [2.18, 20.42]
Wahl 1997	39	74	1	42	0.1%	22.14 [3.15, 155.34]
Wideman 1999 (study 1)	9	60	5	60	0.2%	1.80 [0.64, 5.06]
Subtotal (95% CI)		**1572**		**1118**	**5.6%**	**4.62 [3.85, 5.56]**
Total events	718		101			

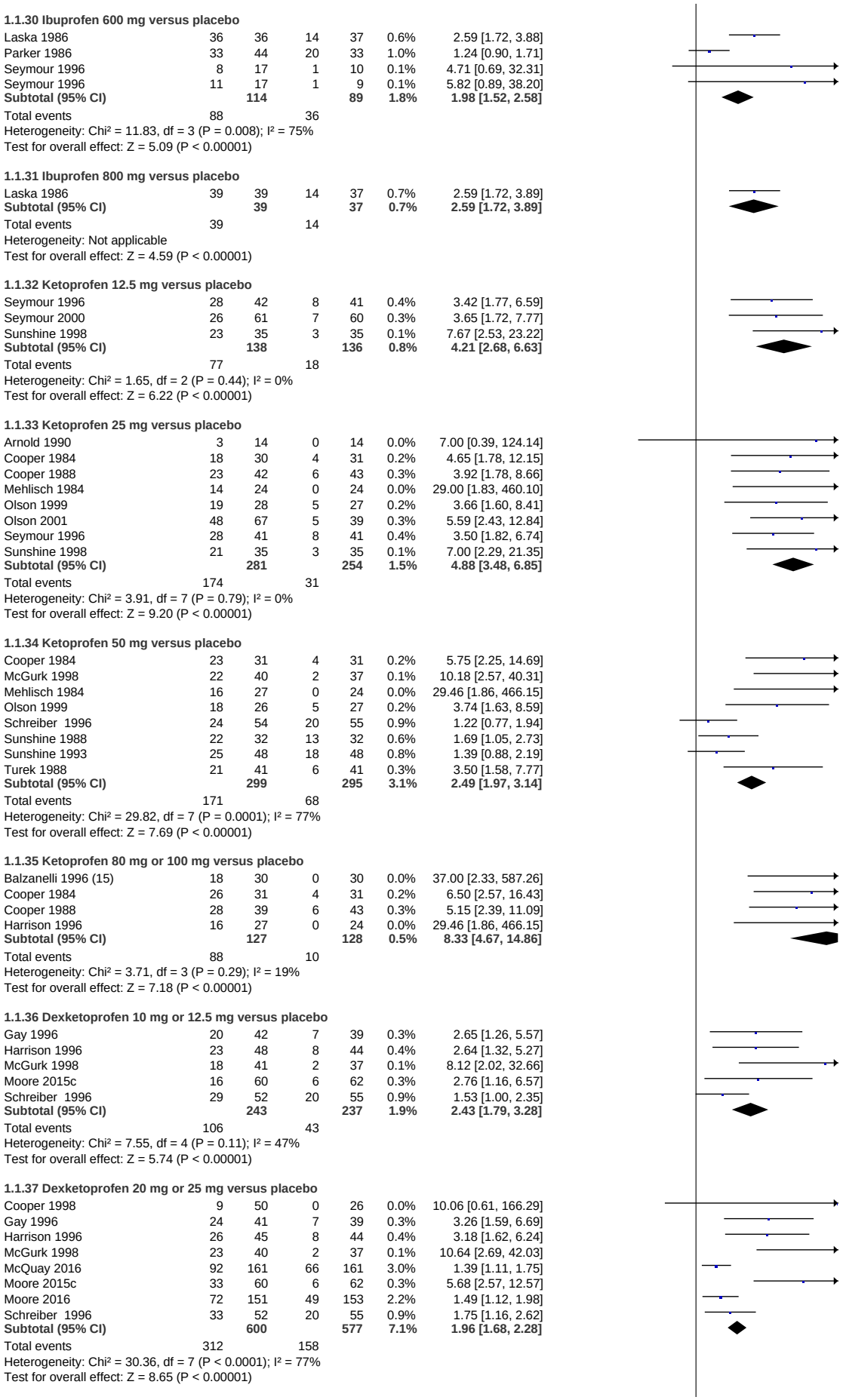
Heterogeneity: Chi² = 58.85, df = 24 (P < 0.0001); I² = 59%
Test for overall effect: Z = 16.32 (P < 0.00001)

1.1.29 Ibuprofen 400 mg versus placebo

Ahlstrom 1993	19	32	2	30	0.1%	8.91 [2.26, 35.02]
Arnold 1990	2	15	0	14	0.0%	4.69 [0.24, 89.88]
Bakshi 1994	57	80	31	82	1.4%	1.88 [1.38, 2.57]
Black 2002	71	100	13	49	0.8%	2.68 [1.65, 4.34]
Black 2002 (9)	71	99	13	50	0.8%	2.76 [1.70, 4.47]
Cheung 2007	40	57	5	57	0.2%	8.00 [3.41, 18.79]
Cooper 1977	20	40	6	40	0.3%	3.33 [1.50, 7.42]
Cooper 1982	22	38	5	46	0.2%	5.33 [2.23, 12.72]
Cooper 1988a	19	37	6	43	0.3%	3.68 [1.64, 8.24]
Cooper 1989	37	61	9	64	0.4%	4.31 [2.28, 8.17]
De Miguel Rivero 1997	24	36	15	34	0.7%	1.51 [0.97, 2.35]
Desjardins 2002	15	52	0	11	0.0%	7.02 [0.45, 109.31]
Desjardins 2002 (10)	16	49	0	12	0.0%	8.58 [0.55, 133.75]
Dionne 1998	26	50	2	25	0.1%	6.50 [1.68, 25.22]
Edwards 2002	145	339	11	339	0.5%	13.18 [7.28, 23.88]
Ehrich 1999	14	20	1	32	0.0%	22.40 [3.19, 157.49]
Forbes 1984	21	28	3	28	0.1%	7.00 [2.35, 20.83]
Forbes 1990	15	32	0	34	0.0%	32.88 [2.05, 527.71]
Forbes 1991b	18	37	3	39	0.1%	6.32 [2.03, 19.71]
Forbes 1992	21	38	0	38	0.0%	43.00 [2.70, 685.19]
Frame 1989	26	42	0	38	0.0%	48.07 [3.03, 762.59]
Fricke 1993	40	81	2	39	0.1%	9.63 [2.45, 37.81]
Gay 1996	26	41	7	39	0.3%	3.53 [1.74, 7.19]
Heidrich 1985	15	40	5	40	0.2%	3.00 [1.20, 7.47]
Hersch 1993a	11	49	0	51	0.0%	23.92 [1.45, 395.20]
Hersch 1993b	9	12	6	16	0.2%	2.00 [0.98, 4.08]
Hersh 2000	47	59	5	27	0.3%	4.30 [1.93, 9.59]
Hill 2001	22	49	5	50	0.2%	4.49 [1.85, 10.91]
Jain 1986	9	49	0	47	0.0%	18.24 [1.09, 304.82]
Jain 1988	33	49	17	48	0.8%	1.90 [1.24, 2.92]
Johnson 1997	15	48	9	48	0.4%	1.67 [0.81, 3.43]
Laska 1986	39	39	14	37	0.7%	2.59 [1.72, 3.89]
Laveneziana 1996	29	42	24	41	1.1%	1.18 [0.85, 1.64]
Malmstrom 1999	33	46	4	45	0.2%	8.07 [3.11, 20.93]
Malmstrom 2002	24	45	0	45	0.0%	49.00 [3.07, 781.94]
Malmstrom 2004	32	48	4	49	0.2%	8.17 [3.13, 21.33]
McQuay 1996	6	30	0	11	0.0%	5.03 [0.31, 82.60]
Mehlisch 1990	124	306	5	85	0.4%	6.89 [2.91, 16.30]
Mehlisch 1995	67	98	1	40	0.1%	27.35 [3.93, 190.30]
Mehlisch 2002 (11)	62	100	7	50	0.4%	4.43 [2.19, 8.95]
Mehlisch 2002	57	100	6	50	0.4%	4.75 [2.20, 10.26]
Morrison 1999	20	51	6	50	0.3%	3.27 [1.43, 7.46]
Nørholt 1998	22	26	8	31	0.3%	3.28 [1.77, 6.09]
Olson 2001	57	67	5	39	0.3%	6.64 [2.91, 15.14]
Pagnoni 1996	13	30	5	32	0.2%	2.77 [1.12, 6.84]
Schachtel 1989	27	36	13	38	0.6%	2.19 [1.36, 3.54]
Schou 1998	41	49	16	56	0.7%	2.93 [1.90, 4.51]
Schwartz 2007	5	15	0	16	0.0%	11.69 [0.70, 194.79]
Seymour 1991 (study 1)	20	31	5	16	0.3%	2.06 [0.95, 4.47]
Seymour 1991 (study 1) (12)	22	32	5	16	0.3%	2.20 [1.03, 4.72]
Seymour 1991 (study 2)	20	30	3	15	0.2%	3.33 [1.17, 9.46]
Seymour 1991 (study 2) (13)	8	30	4	15	0.2%	1.00 [0.36, 2.79]
Seymour 1996 (14)	11	16	1	10	0.1%	6.88 [1.04, 45.44]
Seymour 1996	11	15	1	9	0.1%	6.60 [1.01, 42.95]
Seymour 1998	27	76	3	70	0.1%	8.29 [2.63, 26.12]
Seymour 1999	19	41	7	39	0.3%	2.58 [1.22, 5.45]
Singla 2005	77	175	14	60	0.9%	1.89 [1.16, 3.07]
Sunshine 1983	21	30	3	30	0.1%	7.00 [2.33, 21.00]
Sunshine 1987	16	38	11	40	0.5%	1.53 [0.82, 2.86]
Sunshine 1997	17	40	1	39	0.0%	16.57 [2.32, 118.61]
Van Dyke 2004	112	186	9	62	0.6%	4.15 [2.24, 7.67]
Wideman 1999 (study 2)	21	50	3	51	0.1%	7.14 [2.27, 22.44]
Zelenakas 2004	27	51	6	50	0.3%	4.41 [1.99, 9.76]
Subtotal (95% CI)		**3728**		**2747**	**18.8%**	**3.94 [3.58, 4.35]**
Total events	2013		375			

Heterogeneity: Chi² = 221.50, df = 62 (P < 0.00001); I² = 72%
Test for overall effect: Z = 27.58 (P < 0.00001)





1.1.30 Ibuprofen 600 mg versus placebo

Laska 1986	36	36	14	37	0.6%	2.59 [1.72, 3.88]
Parker 1986	33	44	20	33	1.0%	1.24 [0.90, 1.71]
Seymour 1996	8	17	1	10	0.1%	4.71 [0.69, 32.31]
Seymour 1996	11	17	1	9	0.1%	5.82 [0.89, 38.20]
Subtotal (95% CI)		**114**		**89**	**1.8%**	**1.98 [1.52, 2.58]**
Total events	88		36			

Heterogeneity: Chi² = 11.83, df = 3 (P = 0.008); I² = 75%
Test for overall effect: Z = 5.09 (P < 0.00001)

1.1.31 Ibuprofen 800 mg versus placebo

Laska 1986	39	39	14	37	0.7%	2.59 [1.72, 3.89]
Subtotal (95% CI)		**39**		**37**	**0.7%**	**2.59 [1.72, 3.89]**
Total events	39		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.59 (P < 0.00001)

1.1.32 Ketoprofen 12.5 mg versus placebo

Seymour 1996	28	42	8	41	0.4%	3.42 [1.77, 6.59]
Seymour 2000	26	61	7	60	0.3%	3.65 [1.72, 7.77]
Sunshine 1998	23	35	3	35	0.1%	7.67 [2.53, 23.22]
Subtotal (95% CI)		**138**		**136**	**0.8%**	**4.21 [2.68, 6.63]**
Total events	77		18			

Heterogeneity: Chi² = 1.65, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 6.22 (P < 0.00001)

1.1.33 Ketoprofen 25 mg versus placebo

Arnold 1990	3	14	0	14	0.0%	7.00 [0.39, 124.14]
Cooper 1984	18	30	4	31	0.2%	4.65 [1.78, 12.15]
Cooper 1988	23	42	6	43	0.3%	3.92 [1.78, 8.66]
Mehlisch 1984	14	24	0	24	0.0%	29.00 [1.83, 460.10]
Olson 1999	19	28	5	27	0.2%	3.66 [1.60, 8.41]
Olson 2001	48	67	5	39	0.3%	5.59 [2.43, 12.84]
Seymour 1996	28	41	8	41	0.4%	3.50 [1.82, 6.74]
Sunshine 1998	21	35	3	35	0.1%	7.00 [2.29, 21.35]
Subtotal (95% CI)		**281**		**254**	**1.5%**	**4.88 [3.48, 6.85]**
Total events	174		31			

Heterogeneity: Chi² = 3.91, df = 7 (P = 0.79); I² = 0%
Test for overall effect: Z = 9.20 (P < 0.00001)

1.1.34 Ketoprofen 50 mg versus placebo

Cooper 1984	23	31	4	31	0.2%	5.75 [2.25, 14.69]
McGurk 1998	22	40	2	37	0.1%	10.18 [2.57, 40.31]
Mehlisch 1984	16	27	0	24	0.0%	29.46 [1.86, 466.15]
Olson 1999	18	26	5	27	0.2%	3.74 [1.63, 8.59]
Schreiber 1996	24	54	20	55	0.9%	1.22 [0.77, 1.94]
Sunshine 1988	22	32	13	32	0.6%	1.69 [1.05, 2.73]
Sunshine 1993	25	48	18	48	0.8%	1.39 [0.88, 2.19]
Turek 1988	21	41	6	41	0.3%	3.50 [1.58, 7.77]
Subtotal (95% CI)		**299**		**295**	**3.1%**	**2.49 [1.97, 3.14]**
Total events	171		68			

Heterogeneity: Chi² = 29.82, df = 7 (P = 0.0001); I² = 77%
Test for overall effect: Z = 7.69 (P < 0.00001)

1.1.35 Ketoprofen 80 mg or 100 mg versus placebo

Balzanelli 1996 (15)	18	30	0	30	0.0%	37.00 [2.33, 587.26]
Cooper 1984	26	31	4	31	0.2%	6.50 [2.57, 16.43]
Cooper 1988	28	39	6	43	0.3%	5.15 [2.39, 11.09]
Harrison 1996	16	27	0	24	0.0%	29.46 [1.86, 466.15]
Subtotal (95% CI)		**127**		**128**	**0.5%**	**8.33 [4.67, 14.86]**
Total events	88		10			

Heterogeneity: Chi² = 3.71, df = 3 (P = 0.29); I² = 19%
Test for overall effect: Z = 7.18 (P < 0.00001)

1.1.36 Dexketoprofen 10 mg or 12.5 mg versus placebo

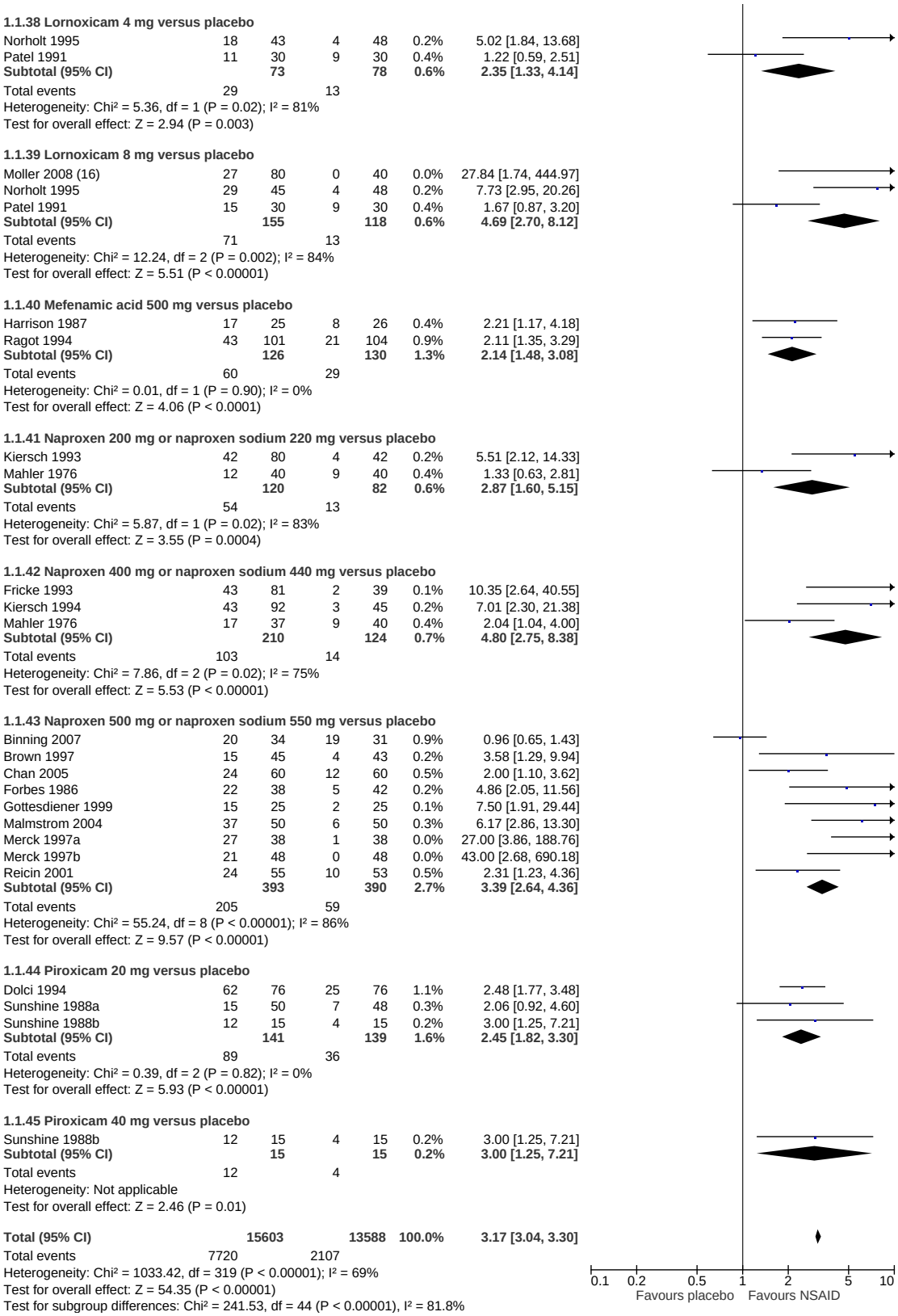
Gay 1996	20	42	7	39	0.3%	2.65 [1.26, 5.57]
Harrison 1996	23	48	8	44	0.4%	2.64 [1.32, 5.27]
McGurk 1998	18	41	2	37	0.1%	8.12 [2.02, 32.66]
Moore 2015c	16	60	6	62	0.3%	2.76 [1.16, 6.57]
Schreiber 1996	29	52	20	55	0.9%	1.53 [1.00, 2.35]
Subtotal (95% CI)		**243**		**237**	**1.9%**	**2.43 [1.79, 3.28]**
Total events	106		43			

Heterogeneity: Chi² = 7.55, df = 4 (P = 0.11); I² = 47%
Test for overall effect: Z = 5.74 (P < 0.00001)

1.1.37 Dexketoprofen 20 mg or 25 mg versus placebo

Cooper 1998	9	50	0	26	0.0%	10.06 [0.61, 166.29]
Gay 1996	24	41	7	39	0.3%	3.26 [1.59, 6.69]
Harrison 1996	26	45	8	44	0.4%	3.18 [1.62, 6.24]
McGurk 1998	23	40	2	37	0.1%	10.64 [2.69, 42.03]
McQuay 2016	92	161	66	161	3.0%	1.39 [1.11, 1.75]
Moore 2015c	33	60	6	62	0.3%	5.68 [2.57, 12.57]
Moore 2016	72	151	49	153	2.2%	1.49 [1.12, 1.98]
Schreiber 1996	33	52	20	55	0.9%	1.75 [1.16, 2.62]
Subtotal (95% CI)		**600**		**577**	**7.1%**	**1.96 [1.68, 2.28]**
Total events	312		158			

Heterogeneity: Chi² = 30.36, df = 7 (P < 0.0001); I² = 77%
Test for overall effect: Z = 8.65 (P < 0.00001)



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Gaskell H, Derry S, Wiffen PJ, Moore RA. Single dose oral ketoprofen or dexketoprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2017, Issue 5. Copyright Cochrane Collaboration, reproduced with permission.

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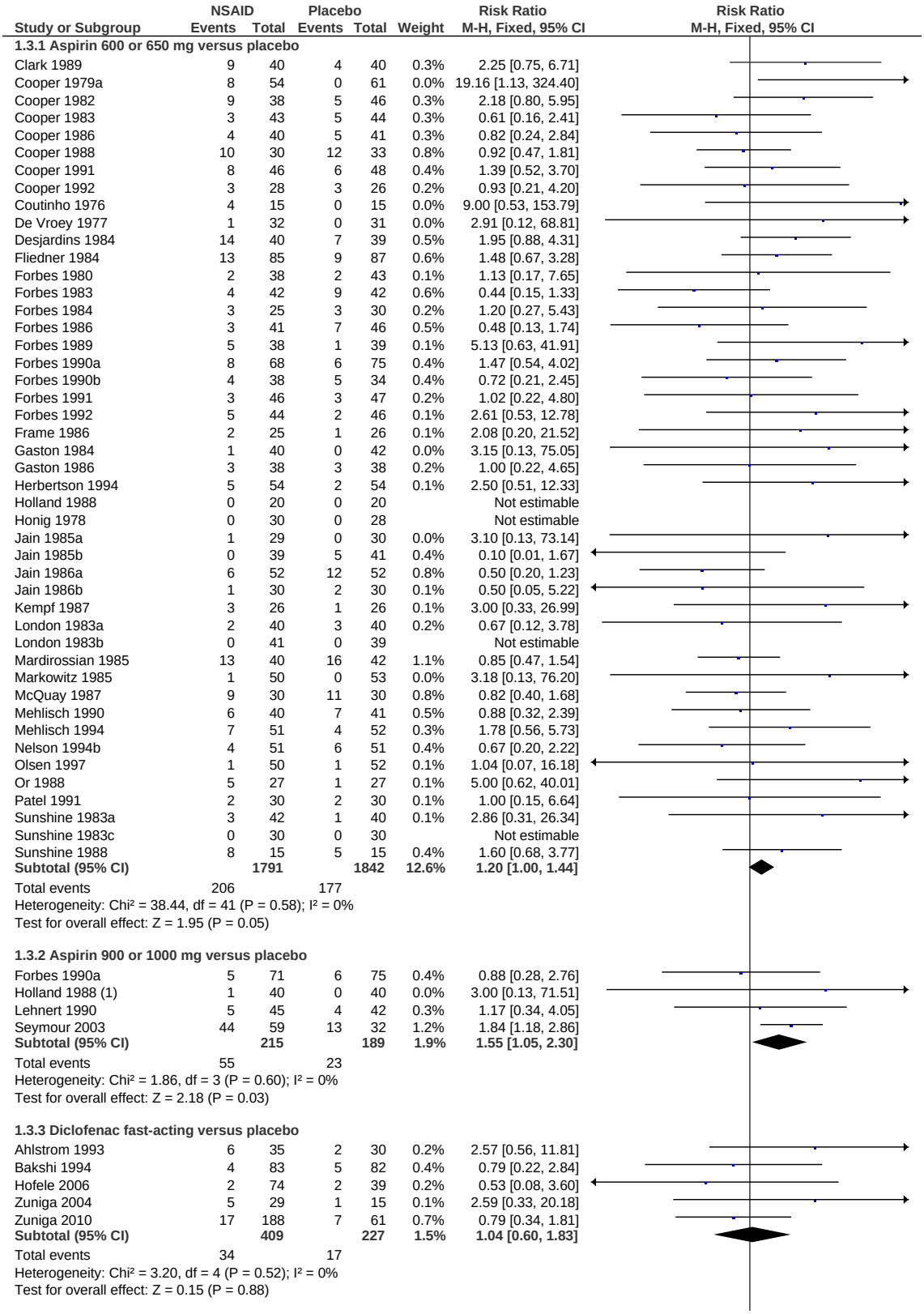
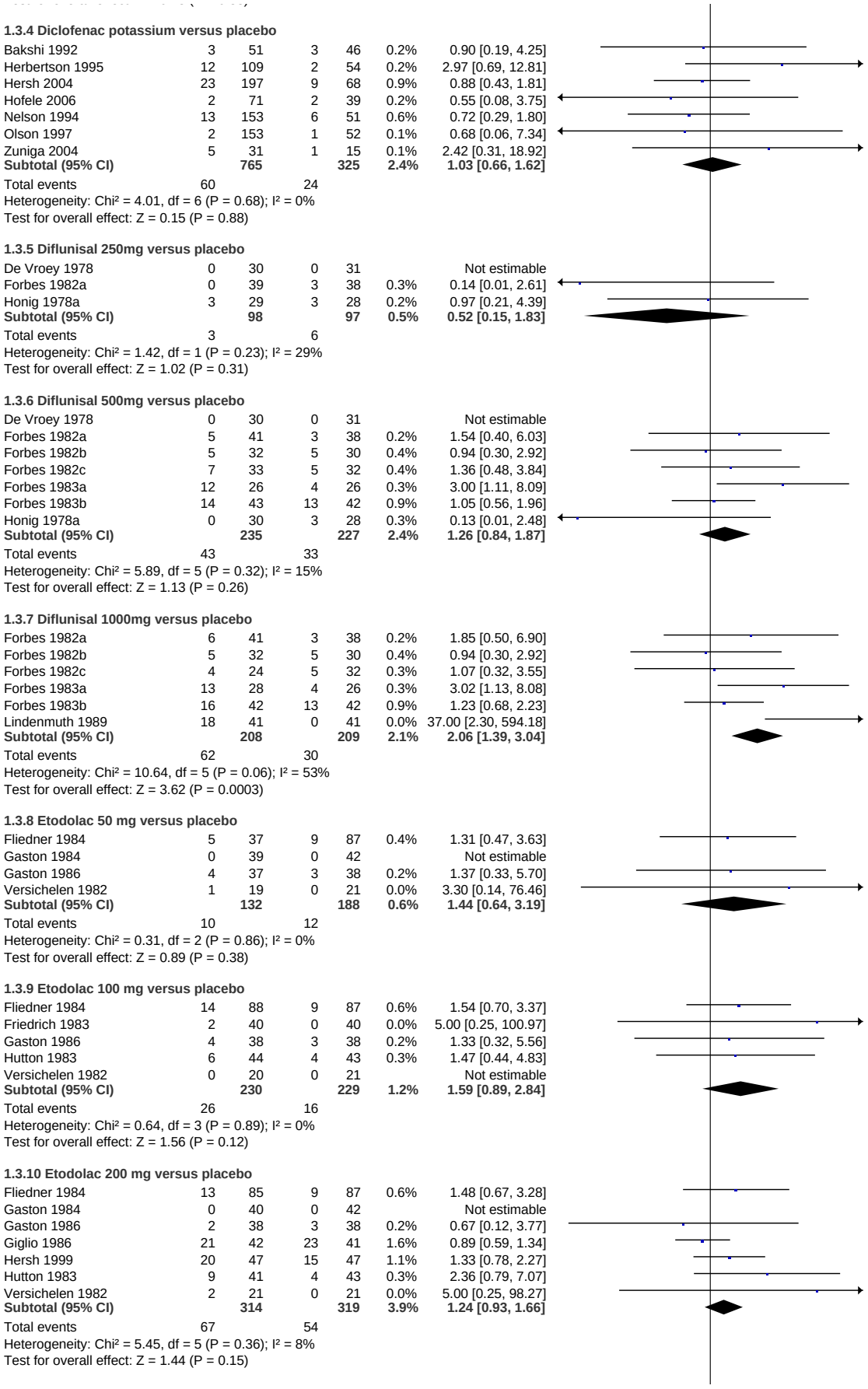
Moll R, Derry S, Moore RA, McQuay HJ. Single dose oral mefenamic acid for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2011, Issue 3. Copyright Cochrane Collaboration, reproduced with permission.

Figure 27: Participants with adverse events





1.3.4 Diclofenac potassium versus placebo

Bakshi 1992	3	51	3	46	0.2%	0.90 [0.19, 4.25]
Herbertson 1995	12	109	2	54	0.2%	2.97 [0.69, 12.81]
Hersh 2004	23	197	9	68	0.9%	0.88 [0.43, 1.81]
Hofele 2006	2	71	2	39	0.2%	0.55 [0.08, 3.75]
Nelson 1994	13	153	6	51	0.6%	0.72 [0.29, 1.80]
Olson 1997	2	153	1	52	0.1%	0.68 [0.06, 7.34]
Zuniga 2004	5	31	1	15	0.1%	2.42 [0.31, 18.92]
Subtotal (95% CI)		**765**		**325**	**2.4%**	**1.03 [0.66, 1.62]**
Total events	60		24			

Heterogeneity: Chi² = 4.01, df = 6 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

1.3.5 Diflunisal 250mg versus placebo

De Vroey 1978	0	30	0	31		Not estimable
Forbes 1982a	0	39	3	38	0.3%	0.14 [0.01, 2.61]
Honig 1978a	3	29	3	28	0.2%	0.97 [0.21, 4.39]
Subtotal (95% CI)		**98**		**97**	**0.5%**	**0.52 [0.15, 1.83]**
Total events	3		6			

Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² = 29%
Test for overall effect: Z = 1.02 (P = 0.31)

1.3.6 Diflunisal 500mg versus placebo

De Vroey 1978	0	30	0	31		Not estimable
Forbes 1982a	5	41	3	38	0.2%	1.54 [0.40, 6.03]
Forbes 1982b	5	32	5	30	0.4%	0.94 [0.30, 2.92]
Forbes 1982c	7	33	5	32	0.4%	1.36 [0.48, 3.84]
Forbes 1983a	12	26	4	26	0.3%	3.00 [1.11, 8.09]
Forbes 1983b	14	43	13	42	0.9%	1.05 [0.56, 1.96]
Honig 1978a	0	30	3	28	0.3%	0.13 [0.01, 2.48]
Subtotal (95% CI)		**235**		**227**	**2.4%**	**1.26 [0.84, 1.87]**
Total events	43		33			

Heterogeneity: Chi² = 5.89, df = 5 (P = 0.32); I² = 15%
Test for overall effect: Z = 1.13 (P = 0.26)

1.3.7 Diflunisal 1000mg versus placebo

Forbes 1982a	6	41	3	38	0.2%	1.85 [0.50, 6.90]
Forbes 1982b	5	32	5	30	0.4%	0.94 [0.30, 2.92]
Forbes 1982c	4	24	5	32	0.3%	1.07 [0.32, 3.55]
Forbes 1983a	13	28	4	26	0.3%	3.02 [1.13, 8.08]
Forbes 1983b	16	42	13	42	0.9%	1.23 [0.68, 2.23]
Lindenmuth 1989	18	41	0	41	0.0%	37.00 [2.30, 594.18]
Subtotal (95% CI)		**208**		**209**	**2.1%**	**2.06 [1.39, 3.04]**
Total events	62		30			

Heterogeneity: Chi² = 10.64, df = 5 (P = 0.06); I² = 53%
Test for overall effect: Z = 3.62 (P = 0.0003)

1.3.8 Etodolac 50 mg versus placebo

Fliedner 1984	5	37	9	87	0.4%	1.31 [0.47, 3.63]
Gaston 1984	0	39	0	42		Not estimable
Gaston 1986	4	37	3	38	0.2%	1.37 [0.33, 5.70]
Versichelen 1982	1	19	0	21	0.0%	3.30 [0.14, 76.46]
Subtotal (95% CI)		**132**		**188**	**0.6%**	**1.44 [0.64, 3.19]**
Total events	10		12			

Heterogeneity: Chi² = 0.31, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.38)

1.3.9 Etodolac 100 mg versus placebo

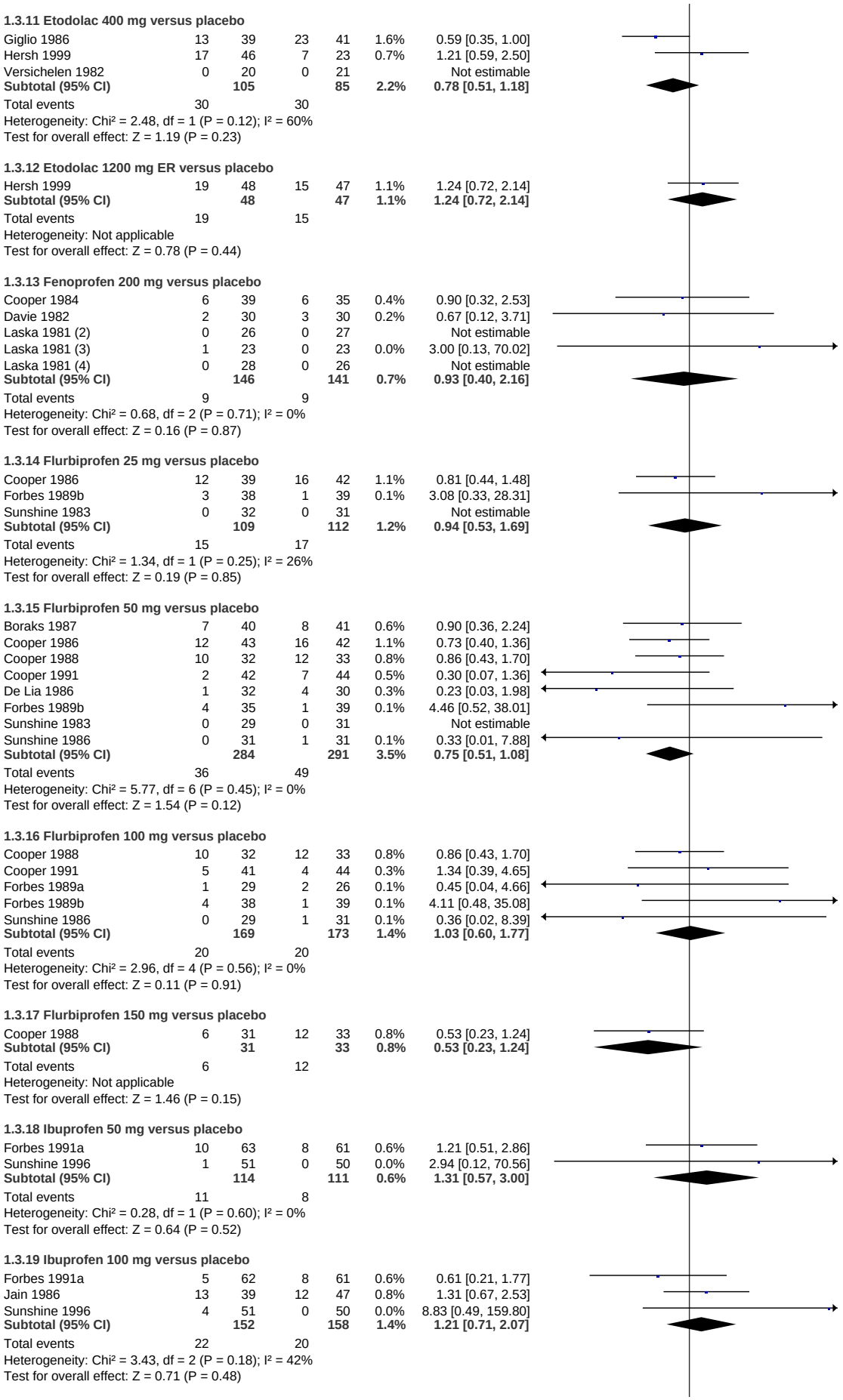
Fliedner 1984	14	88	9	87	0.6%	1.54 [0.70, 3.37]
Friedrich 1983	2	40	0	40	0.0%	5.00 [0.25, 100.97]
Gaston 1986	4	38	3	38	0.2%	1.33 [0.32, 5.56]
Hutton 1983	6	44	4	43	0.3%	1.47 [0.44, 4.83]
Versichelen 1982	0	20	0	21		Not estimable
Subtotal (95% CI)		**230**		**229**	**1.2%**	**1.59 [0.89, 2.84]**
Total events	26		16			

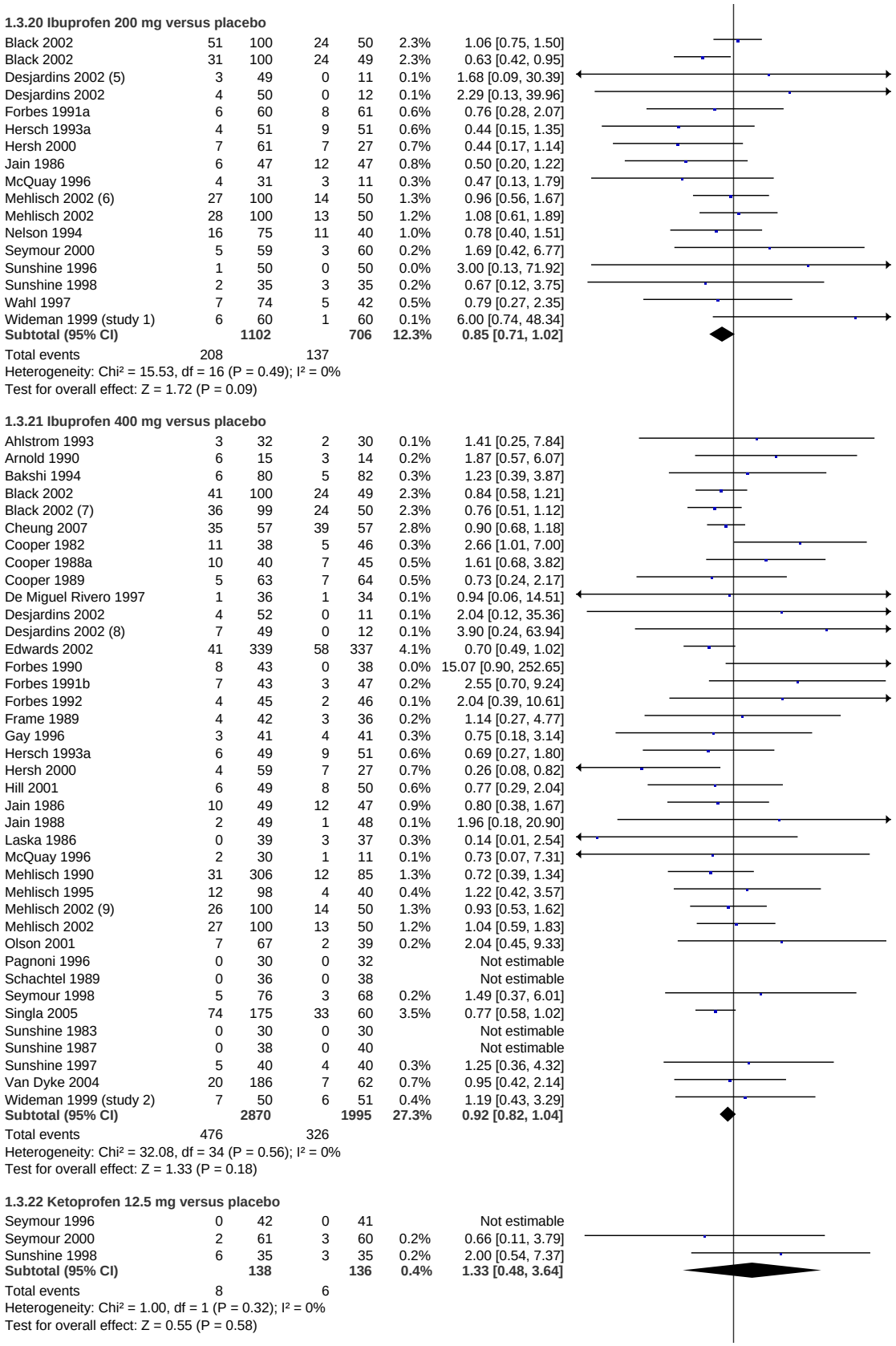
Heterogeneity: Chi² = 0.64, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)

1.3.10 Etodolac 200 mg versus placebo

Fliedner 1984	13	85	9	87	0.6%	1.48 [0.67, 3.28]
Gaston 1984	0	40	0	42		Not estimable
Gaston 1986	2	38	3	38	0.2%	0.67 [0.12, 3.77]
Giglio 1986	21	42	23	41	1.6%	0.89 [0.59, 1.34]
Hersh 1999	20	47	15	47	1.1%	1.33 [0.78, 2.27]
Hutton 1983	9	41	4	43	0.3%	2.36 [0.79, 7.07]
Versichelen 1982	2	21	0	21	0.0%	5.00 [0.25, 98.27]
Subtotal (95% CI)		**314**		**319**	**3.9%**	**1.24 [0.93, 1.66]**
Total events	67		54			

Heterogeneity: Chi² = 5.45, df = 5 (P = 0.36); I² = 8%
Test for overall effect: Z = 1.44 (P = 0.15)





1.3.20 Ibuprofen 200 mg versus placebo

Black 2002	51	100	24	50	2.3%	1.06 [0.75, 1.50]
Black 2002	31	100	24	49	2.3%	0.63 [0.42, 0.95]
Desjardins 2002 (5)	3	49	0	11	0.1%	1.68 [0.09, 30.39]
Desjardins 2002	4	50	0	12	0.1%	2.29 [0.13, 39.96]
Forbes 1991a	6	60	8	61	0.6%	0.76 [0.28, 2.07]
Hersch 1993a	4	51	9	51	0.6%	0.44 [0.15, 1.35]
Hersh 2000	7	61	7	27	0.7%	0.44 [0.17, 1.14]
Jain 1986	6	47	12	47	0.8%	0.50 [0.20, 1.22]
McQuay 1996	4	31	3	11	0.3%	0.47 [0.13, 1.79]
Mehlisch 2002 (6)	27	100	14	50	1.3%	0.96 [0.56, 1.67]
Mehlisch 2002	28	100	13	50	1.2%	1.08 [0.61, 1.89]
Nelson 1994	16	75	11	40	1.0%	0.78 [0.40, 1.51]
Seymour 2000	5	59	3	60	0.2%	1.69 [0.42, 6.77]
Sunshine 1996	1	50	0	50	0.0%	3.00 [0.13, 71.92]
Sunshine 1998	2	35	3	35	0.2%	0.67 [0.12, 3.75]
Wahl 1997	7	74	5	42	0.5%	0.79 [0.27, 2.35]
Wideman 1999 (study 1)	6	60	1	60	0.1%	6.00 [0.74, 48.34]
Subtotal (95% CI)		**1102**		**706**	**12.3%**	**0.85 [0.71, 1.02]**
Total events	208		137			

Heterogeneity: Chi² = 15.53, df = 16 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)

1.3.21 Ibuprofen 400 mg versus placebo

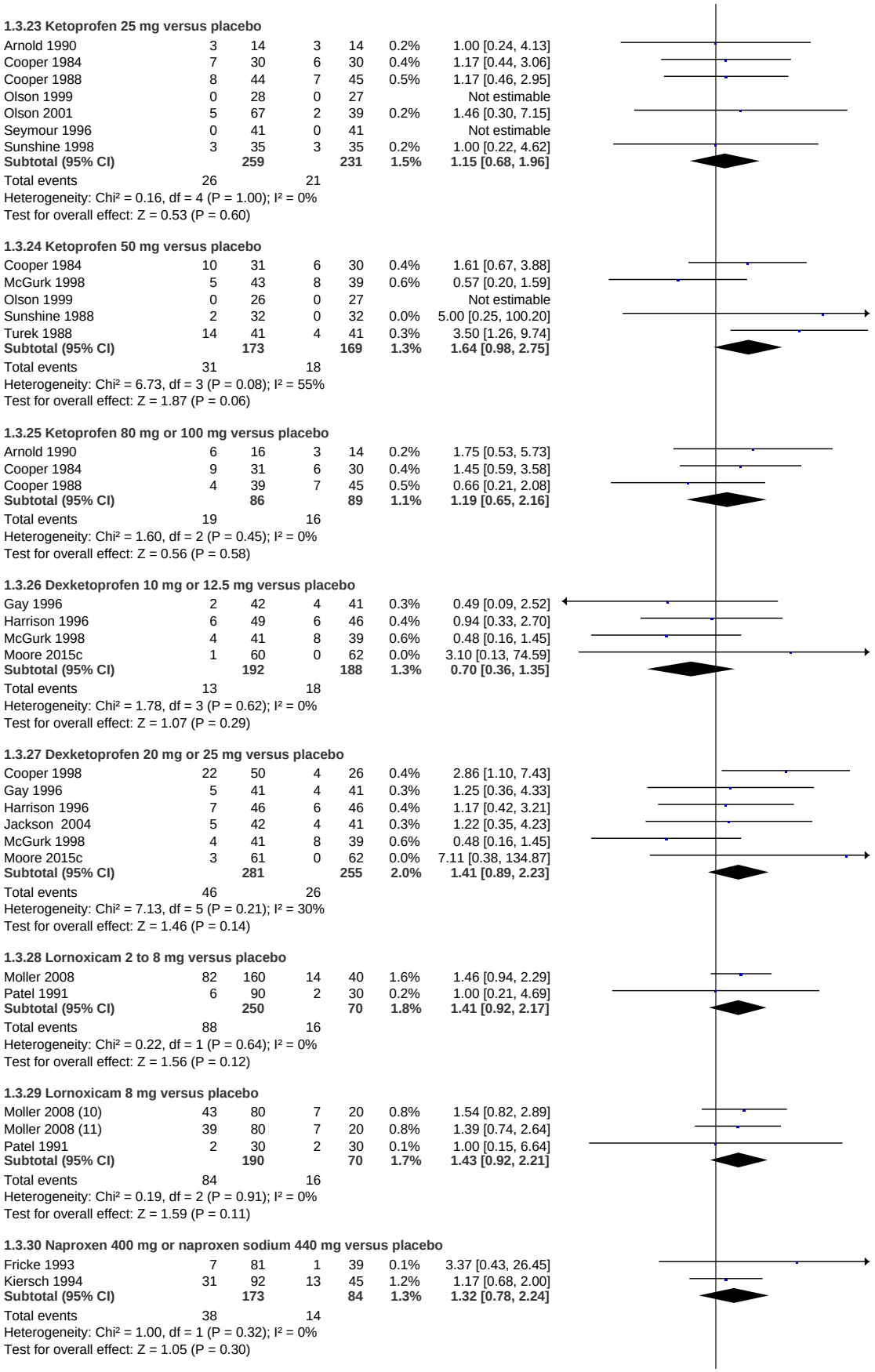
Ahlstrom 1993	3	32	2	30	0.1%	1.41 [0.25, 7.84]
Arnold 1990	6	15	3	14	0.2%	1.87 [0.57, 6.07]
Bakshi 1994	6	80	5	82	0.3%	1.23 [0.39, 3.87]
Black 2002	41	100	24	49	2.3%	0.84 [0.58, 1.21]
Black 2002 (7)	36	99	24	50	2.3%	0.76 [0.51, 1.12]
Cheung 2007	35	57	39	57	2.8%	0.90 [0.68, 1.18]
Cooper 1982	11	38	5	46	0.3%	2.66 [1.01, 7.00]
Cooper 1988a	10	40	7	45	0.5%	1.61 [0.68, 3.82]
Cooper 1989	5	63	7	64	0.5%	0.73 [0.24, 2.17]
De Miguel Rivero 1997	1	36	1	34	0.1%	0.94 [0.06, 14.51]
Desjardins 2002	4	52	0	11	0.1%	2.04 [0.12, 35.36]
Desjardins 2002 (8)	7	49	0	12	0.1%	3.90 [0.24, 63.94]
Edwards 2002	41	339	58	337	4.1%	0.70 [0.49, 1.02]
Forbes 1990	8	43	0	38	0.0%	15.07 [0.90, 252.65]
Forbes 1991b	7	43	3	47	0.2%	2.55 [0.70, 9.24]
Forbes 1992	4	45	2	46	0.1%	2.04 [0.39, 10.61]
Frame 1989	4	42	3	36	0.2%	1.14 [0.27, 4.77]
Gay 1996	3	41	4	41	0.3%	0.75 [0.18, 3.14]
Hersch 1993a	6	49	9	51	0.6%	0.69 [0.27, 1.80]
Hersh 2000	4	59	7	27	0.7%	0.26 [0.08, 0.82]
Hill 2001	6	49	8	50	0.6%	0.77 [0.29, 2.04]
Jain 1986	10	49	12	47	0.9%	0.80 [0.38, 1.67]
Jain 1988	2	49	1	48	0.1%	1.96 [0.18, 20.90]
Laska 1986	0	39	3	37	0.3%	0.14 [0.01, 2.54]
McQuay 1996	2	30	1	11	0.1%	0.73 [0.07, 7.31]
Mehlisch 1990	31	306	12	85	1.3%	0.72 [0.39, 1.34]
Mehlisch 1995	12	98	4	40	0.4%	1.22 [0.42, 3.57]
Mehlisch 2002 (9)	26	100	14	50	1.3%	0.93 [0.53, 1.62]
Mehlisch 2002	27	100	13	50	1.2%	1.04 [0.59, 1.83]
Olson 2001	7	67	2	39	0.2%	2.04 [0.45, 9.33]
Pagnoni 1996	0	30	0	32		Not estimable
Schachtel 1989	0	36	0	38		Not estimable
Seymour 1998	5	76	3	68	0.2%	1.49 [0.37, 6.01]
Singla 2005	74	175	33	60	3.5%	0.77 [0.58, 1.02]
Sunshine 1983	0	30	0	30		Not estimable
Sunshine 1987	0	38	0	40		Not estimable
Sunshine 1997	5	40	4	40	0.3%	1.25 [0.36, 4.32]
Van Dyke 2004	20	186	7	62	0.7%	0.95 [0.42, 2.14]
Wideman 1999 (study 2)	7	50	6	51	0.4%	1.19 [0.43, 3.29]
Subtotal (95% CI)		**2870**		**1995**	**27.3%**	**0.92 [0.82, 1.04]**
Total events	476		326			

Heterogeneity: Chi² = 32.08, df = 34 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)

1.3.22 Ketoprofen 12.5 mg versus placebo

Seymour 1996	0	42	0	41		Not estimable
Seymour 2000	2	61	3	60	0.2%	0.66 [0.11, 3.79]
Sunshine 1998	6	35	3	35	0.2%	2.00 [0.54, 7.37]
Subtotal (95% CI)		**138**		**136**	**0.4%**	**1.33 [0.48, 3.64]**
Total events	8		6			

Heterogeneity: Chi² = 1.00, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)



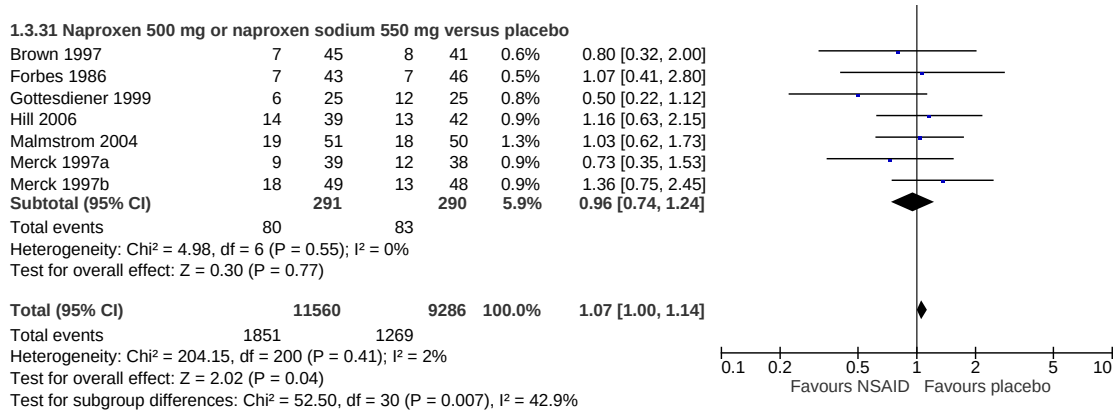


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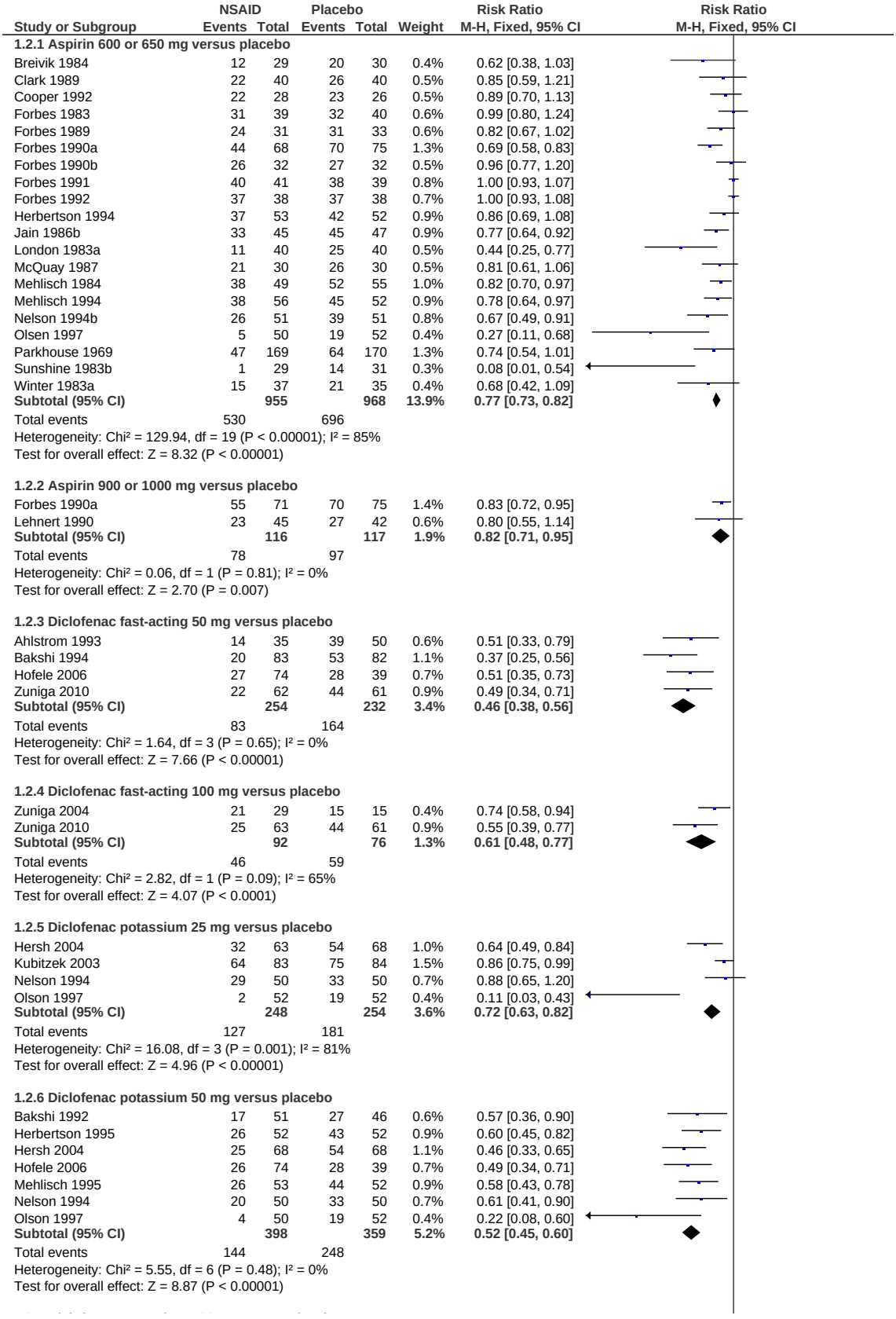
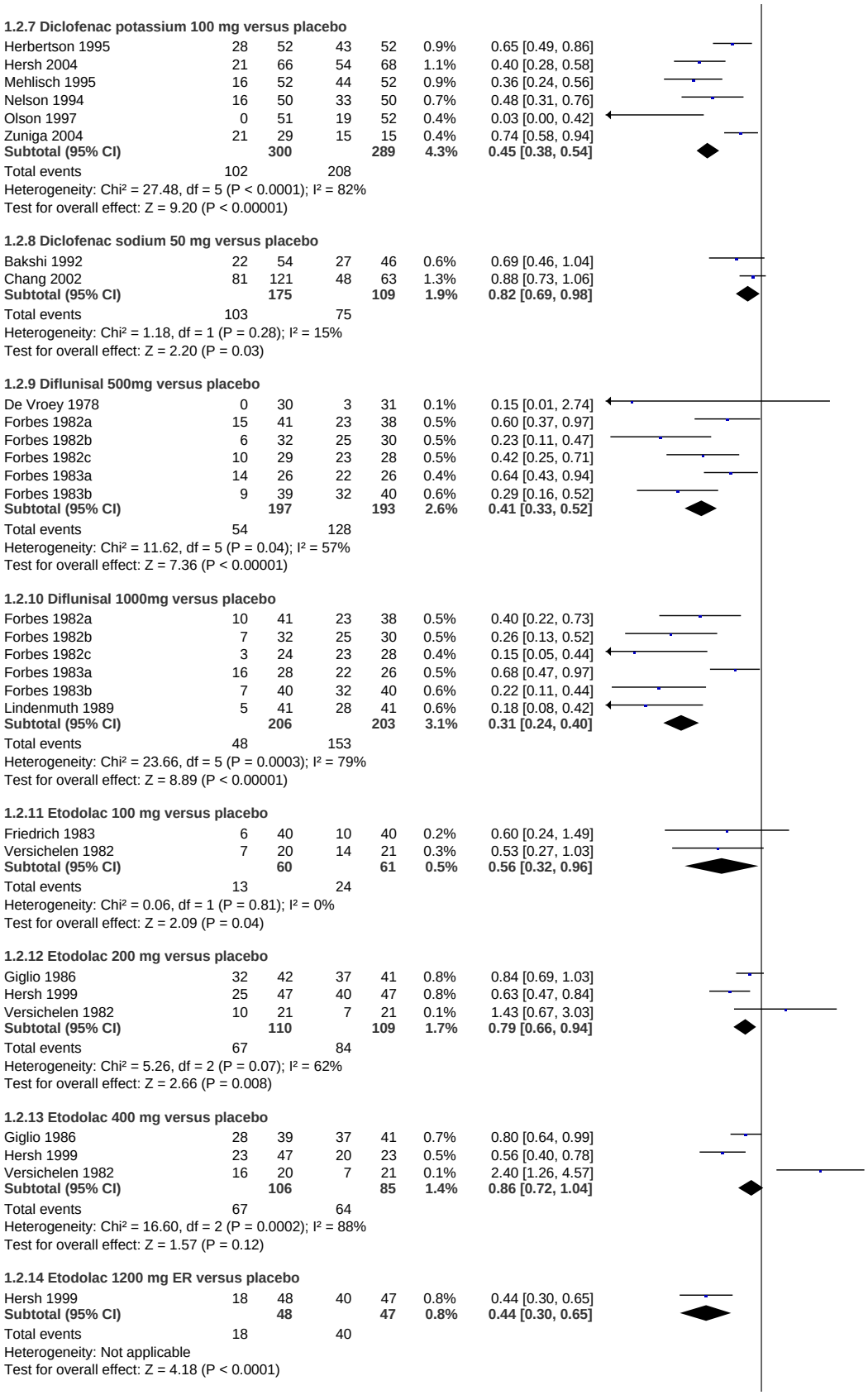
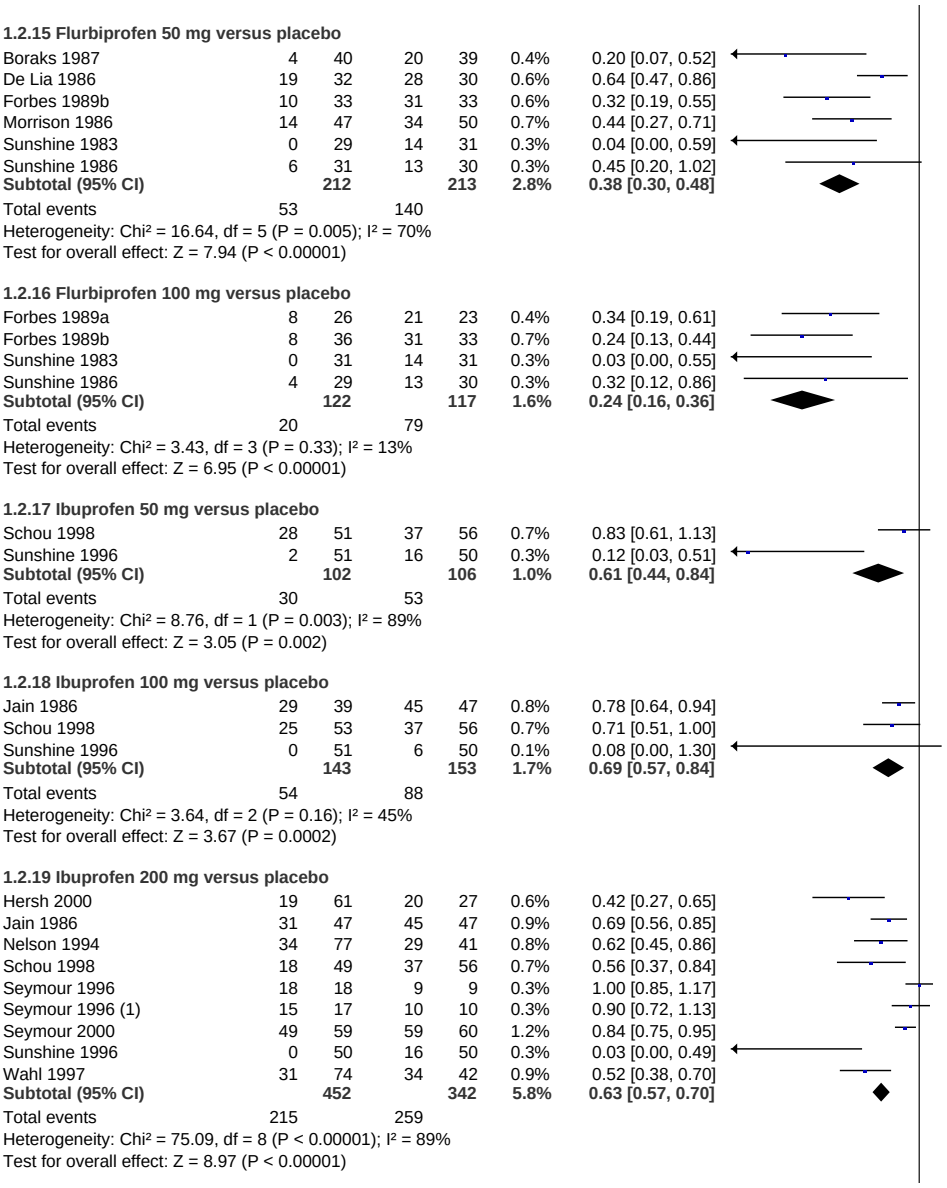
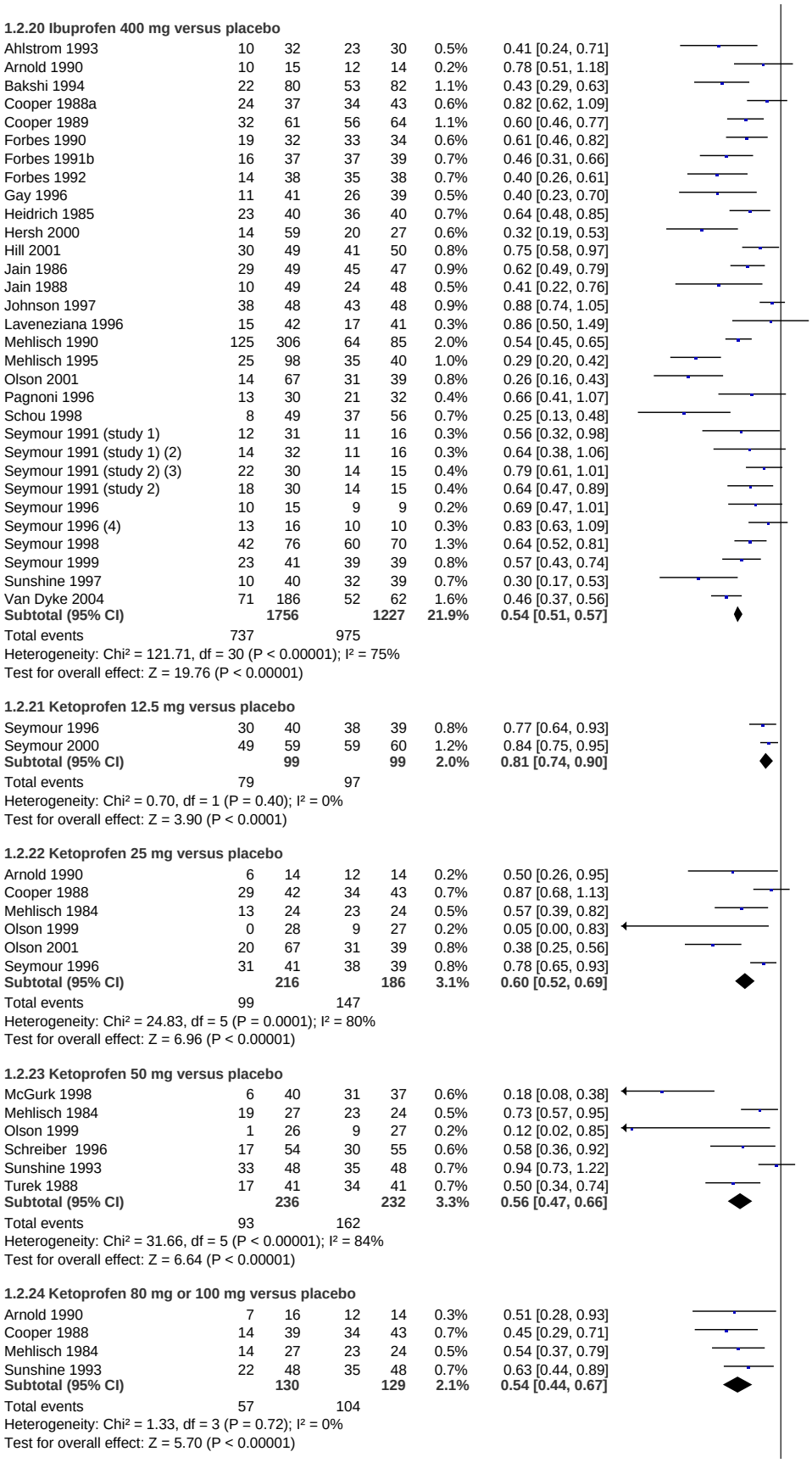
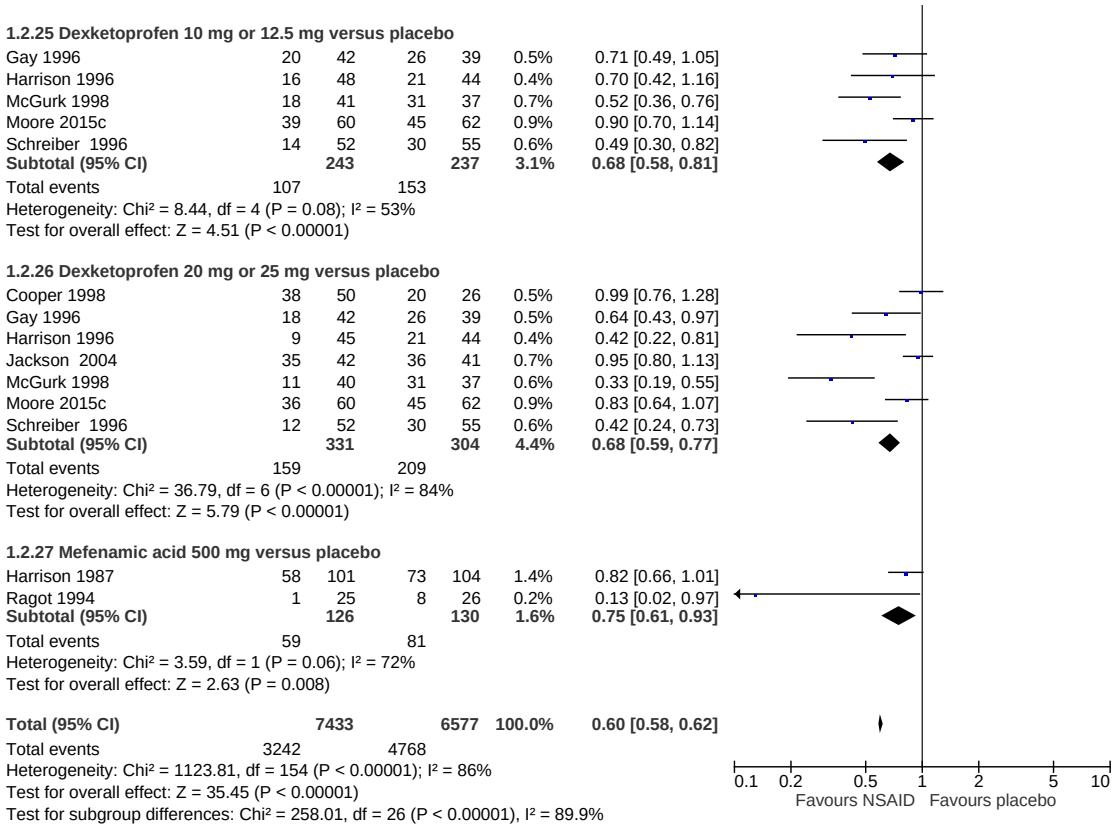
Figure 28: Participants using rescue medication at 6 hours











Footnotes
(1) ibuprofen soluble
(2) ibuprofen liquigel
(3) ibuprofen soluble
(4) ibuprofen soluble

Source: *Derry S, Moore RA. Single dose oral aspirin for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 4. Copyright Cochrane Collaboration, reproduced with permission.*

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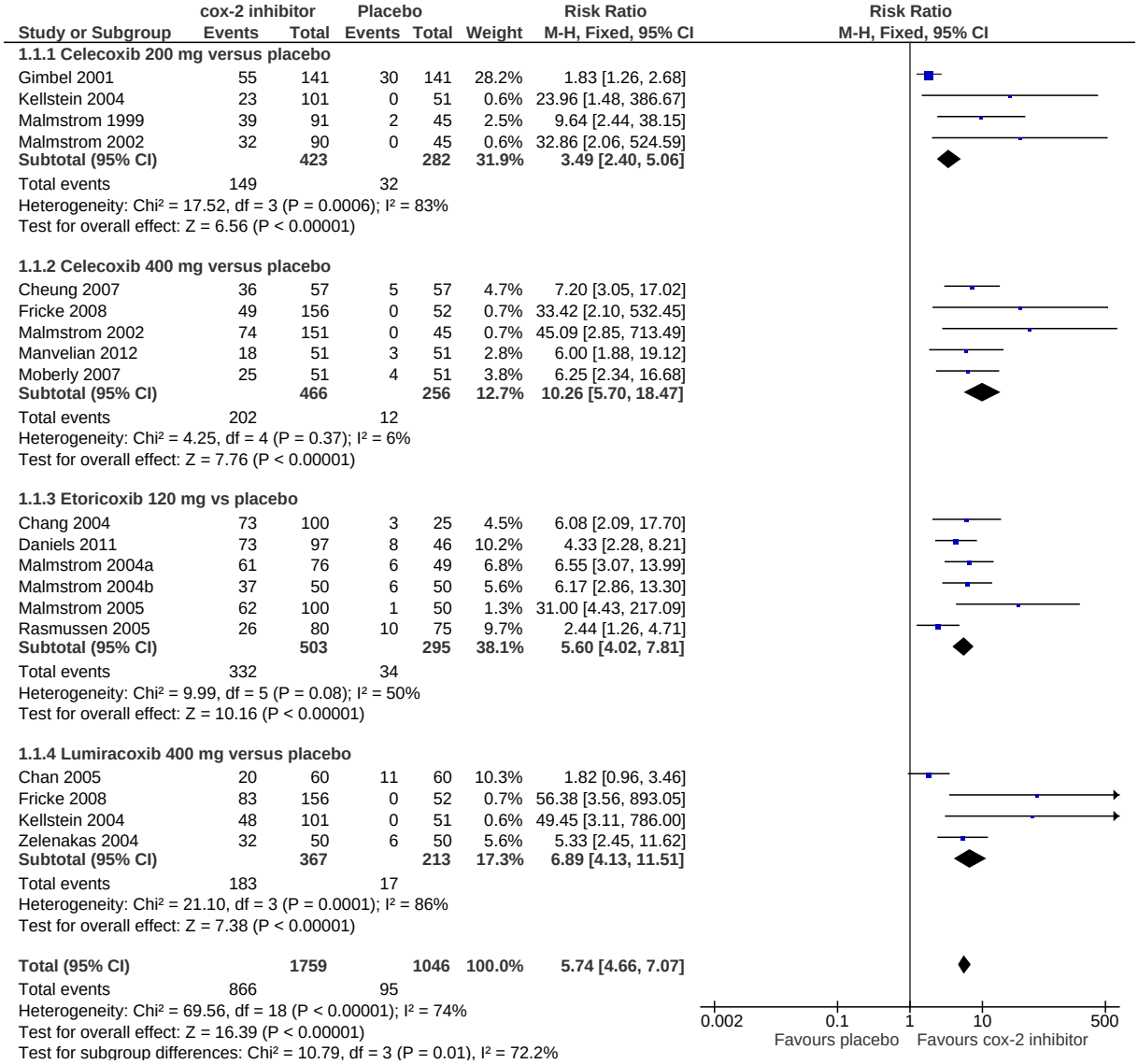
Moll R, Derry S, Moore RA, McQuay HJ. Single dose oral mefenamic acid for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2011, Issue 3. Copyright Cochrane Collaboration, reproduced with permission.

1

D.2 Cox-2 versus placebo

Figure 29: Participants with at least 50% pain relief over 6 hours



Source: *Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 10. Copyright Cochrane Collaboration, reproduced with permission.*

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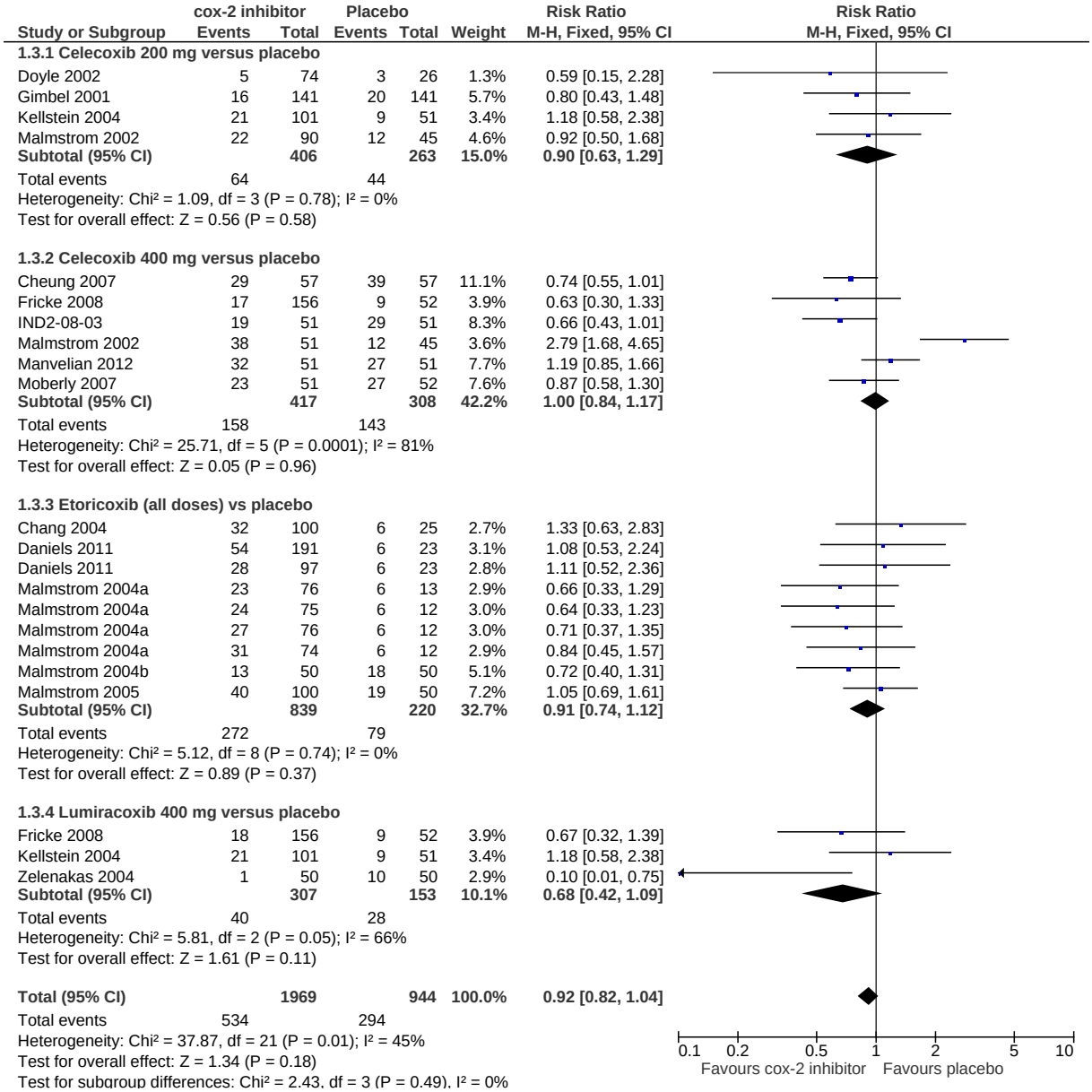
Roy YM, Derry S, Moore RA. Single dose oral lumiracoxib for postoperative pain in adults. Cochrane Database of Systematic Reviews 2010, Issue 7. Copyright Cochrane Collaboration, reproduced with permission.

Figure 30: Participants with adverse events



Source: *Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 10. Copyright Cochrane Collaboration, reproduced with permission.*

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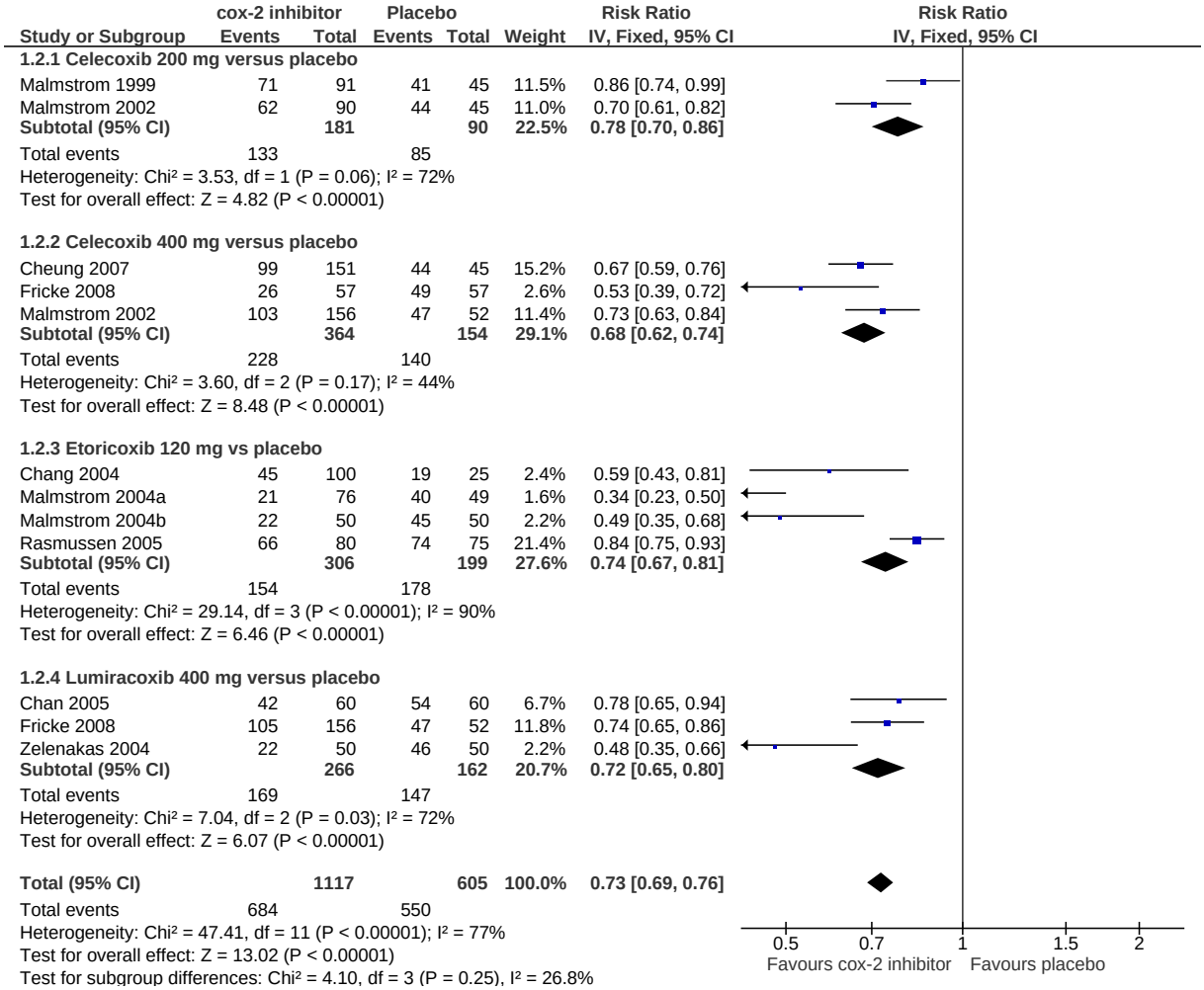
Roy YM, Derry S, Moore RA. Single dose oral lumiracoxib for postoperative pain in adults. Cochrane Database of Systematic Reviews 2010, Issue 7. Copyright Cochrane Collaboration, reproduced with permission.

Figure 31: Participants using rescue medication



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Roy YM, Derry S, Moore RA. Single dose oral lumiracoxib for postoperative pain in adults. Cochrane Database of Systematic Reviews 2010, Issue 7. Copyright Cochrane Collaboration, reproduced with permission.

1

D.3 Naproxen versus Ibuprofen

Figure 32: Total pain relief at 6 hours

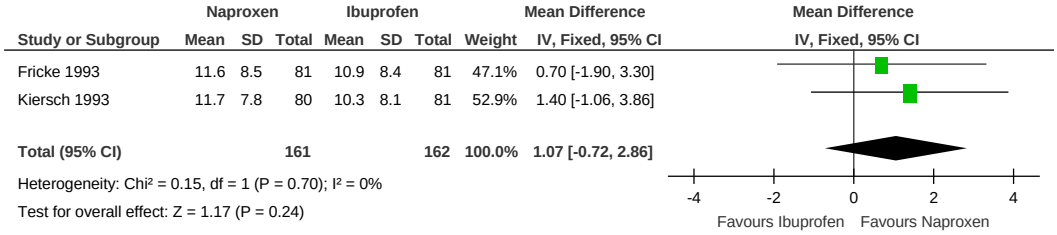


Figure 33: Total pain relief ≥ 6 – 24 hours

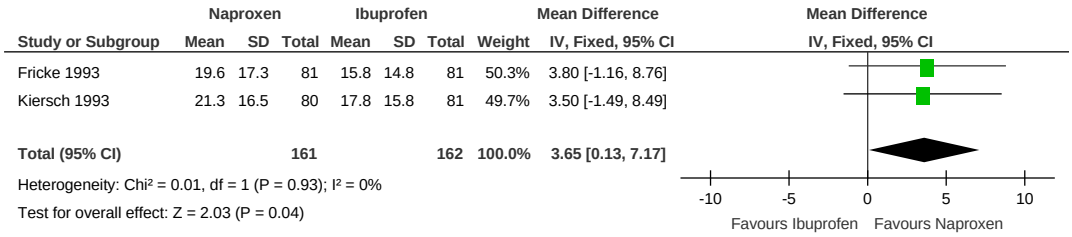
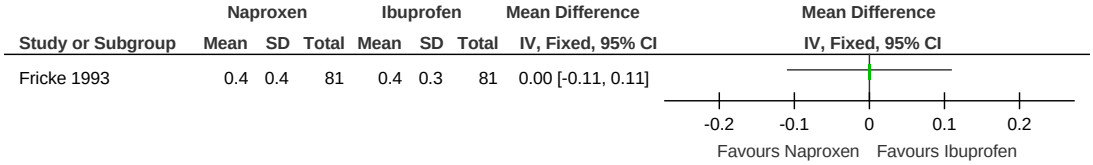


Figure 34: Pain relief (50% resolved)



D.4 Ketorolac versus Diclofenac

Figure 35: Pain score ≤ 6 hours

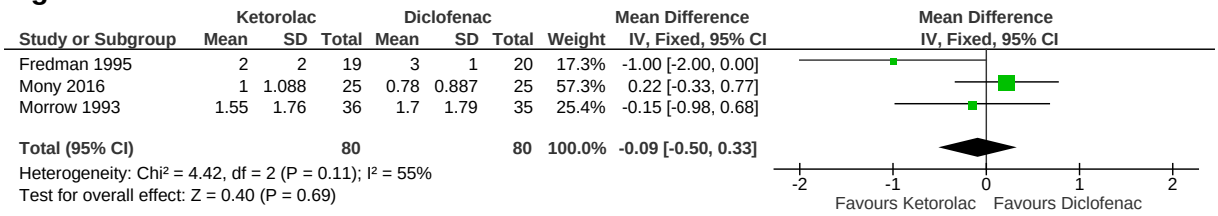
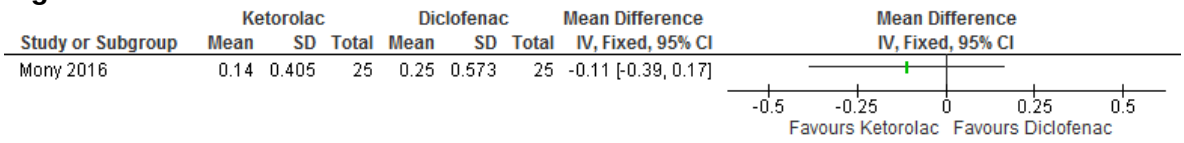


Figure 36: Pain score ≥ 6 – 24 hours

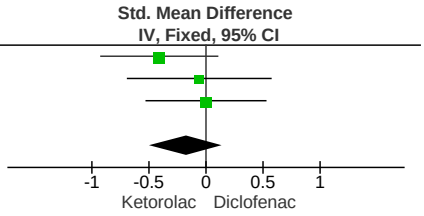


1

Figure 37: Dose of opioid ≤ 6 hours

Study or Subgroup	Ketorolac Mean	SD	Total	Diclofenac Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Aftab 2008	1.3	3.01	30	2.57	3.11	30	38.2%	-0.41 [-0.92, 0.10]
Fredman 1995	8.6	5.2	19	8.9	4.8	20	25.4%	-0.06 [-0.69, 0.57]
Kostamvaara 1998	60	40	28	60	30	28	36.4%	0.00 [-0.52, 0.52]
Total (95% CI)			**77**			**78**	**100.0%**	**-0.17 [-0.49, 0.14]**

Heterogeneity: Chi² = 1.37, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)

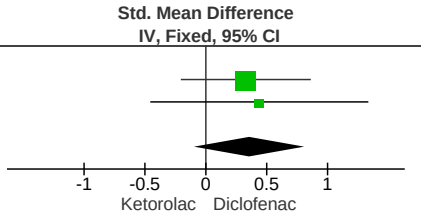


2

Figure 38: Dose of opioid ≥ 6 – 24 hours

Study or Subgroup	Ketorolac Mean	SD	Total	Diclofenac Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Aftab 2008	0	0	30	0	0	30		Not estimable
Kostamvaara 1998	50	30	28	40	30	28	74.0%	0.33 [-0.20, 0.86]
Perttunen 1999	31.6	32.4	10	21	4	10	26.0%	0.44 [-0.45, 1.33]
Total (95% CI)			**68**			**68**	**100.0%**	**0.36 [-0.10, 0.81]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)

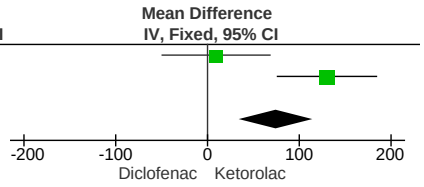


3

Figure 39: Total Pain relief (6 hours)

Study or Subgroup	Ketorolac Mean	SD	Total	Diclofenac Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Canadell-Carafi 1990	421.1	122.2	37	411.7	138.8	39	45.7%	9.40 [-49.32, 68.12]
Christensen 2011	400.3	170.58	47	270.1	187.2	255	54.3%	130.20 [76.29, 184.11]
Total (95% CI)			**84**			**294**	**100.0%**	**74.95 [35.24, 114.66]**

Heterogeneity: Chi² = 8.82, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 3.70 (P = 0.0002)



4

Figure 40: Mortality

Study or Subgroup	Ketorolac Events	Total	Diclofenac Events	Total	Risk Ratio M-H, Fixed, 95% CI
Forrest 2002	9	2576	5	2568	1.79 [0.60, 5.35]

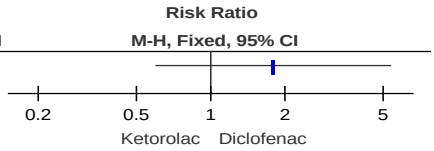


Figure 41: Acute Kidney Injury

Study or Subgroup	Ketorolac Events	Total	Diclofenac Events	Total	Risk Ratio M-H, Fixed, 95% CI
Forrest 2002	2	2576	4	2568	0.50 [0.09, 2.72]

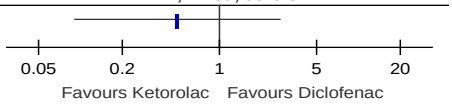


Figure 42: Surgical site bleed

Study or Subgroup	Ketorolac Events	Total	Diclofenac Events	Total	Risk Ratio M-H, Fixed, 95% CI
Forrest 2002	39	2576	37	2568	1.05 [0.67, 1.64]

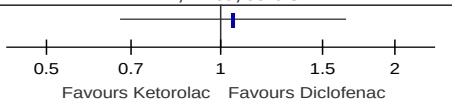


Figure 43: Gastrointestinal bleed

Study or Subgroup	Ketorolac Events	Ketorolac Total	Diclofenac Events	Diclofenac Total	Risk Ratio M-H, Fixed, 95% CI
Forrest 2002	0	2576	1	2568	0.33 [0.01, 8.15]

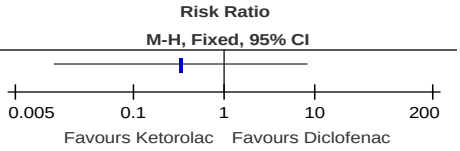


Figure 44: Allergic reaction

Study or Subgroup	Ketorolac Events	Ketorolac Total	Diclofenac Events	Diclofenac Total	Risk Ratio M-H, Fixed, 95% CI
Forrest 2002	3	2576	3	2568	1.00 [0.20, 4.93]

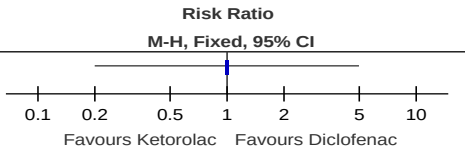
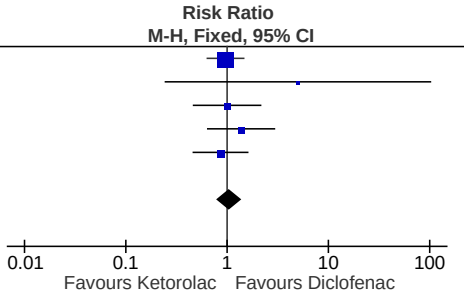


Figure 45: Nausea

Study or Subgroup	Ketorolac Events	Ketorolac Total	Diclofenac Events	Diclofenac Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gan 2012	22	67	48	141	52.3%	0.96 [0.64, 1.46]
Jakobsson 1996	2	50	0	50	0.8%	5.00 [0.25, 101.58]
Kostamvaara 1998	9	28	9	28	15.2%	1.00 [0.47, 2.14]
Tarkkila 1996	11	30	8	30	13.5%	1.38 [0.64, 2.93]
Tarkkila 1999	9	19	11	20	18.1%	0.86 [0.46, 1.60]
Total (95% CI)		**194**		**269**	**100.0%**	**1.04 [0.78, 1.39]**
Total events	53		76			

Heterogeneity: Chi² = 2.07, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)

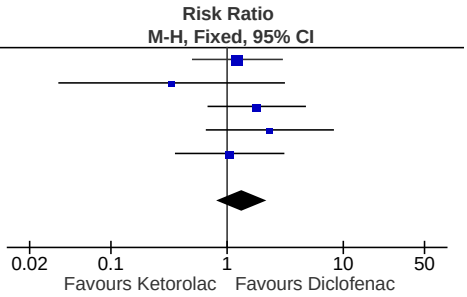


1

Figure 46: Vomiting

Study or Subgroup	Ketorolac Events	Ketorolac Total	Diclofenac Events	Diclofenac Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gan 2012	7	67	12	141	32.8%	1.23 [0.51, 2.98]
Jakobsson 1996	1	50	3	50	12.7%	0.33 [0.04, 3.10]
Kostamvaara 1998	9	28	5	28	21.2%	1.80 [0.69, 4.70]
Tarkkila 1996	7	30	3	30	12.7%	2.33 [0.67, 8.18]
Tarkkila 1999	5	19	5	20	20.6%	1.05 [0.36, 3.07]
Total (95% CI)		**194**		**269**	**100.0%**	**1.34 [0.82, 2.18]**
Total events	29		28			

Heterogeneity: Chi² = 2.84, df = 4 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)

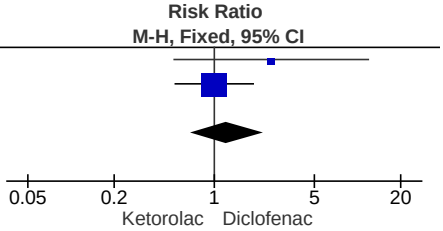


2

Figure 47: Nausea & Vomiting

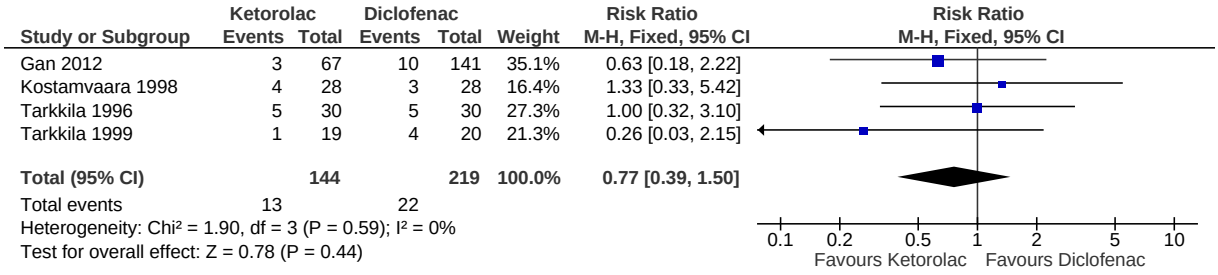
Study or Subgroup	Ketorolac Events	Ketorolac Total	Diclofenac Events	Diclofenac Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aftab 2008	5	30	2	30	15.4%	2.50 [0.53, 11.89]
Chui 1995	11	25	11	25	84.6%	1.00 [0.54, 1.87]
Total (95% CI)		**55**		**55**	**100.0%**	**1.23 [0.68, 2.21]**
Total events	16		13			

Heterogeneity: Chi² = 1.22, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 0.69 (P = 0.49)



3

Figure 48: Itching



1

Figure 49: Headache

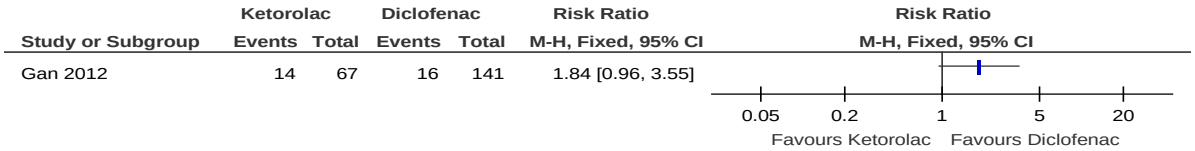
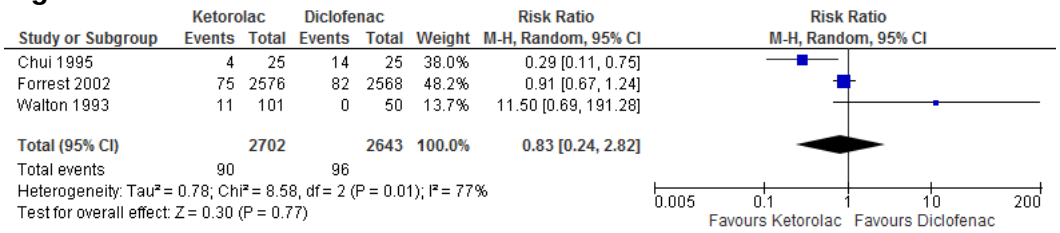
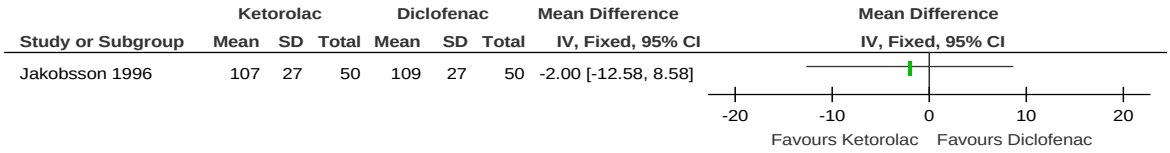


Figure 50: Other adverse events



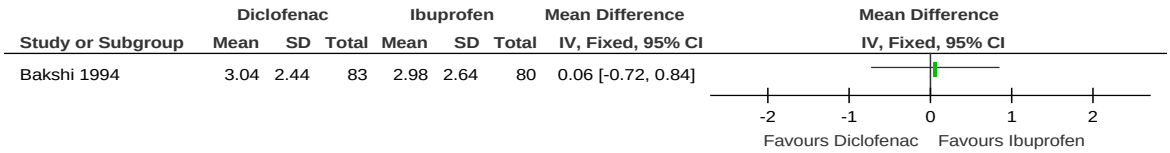
2

Figure 51: Length of stay



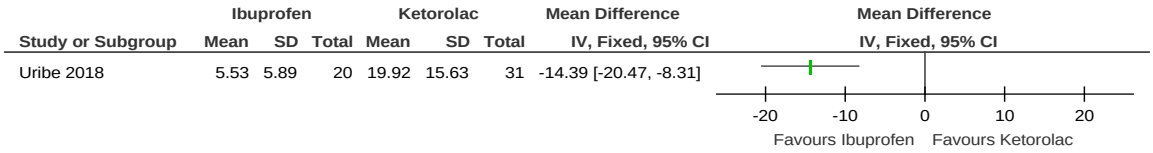
3 # D.5 Diclofenac versus Ibuprofen

Figure 52: Pain score ≤ 6 hours



D.6 Ibuprofen versus Ketorolac

Figure 53: Dose of opioid ≤ 6 hours



D.7 Ketorolac versus Parecoxib

Figure 54: Pain score ≤ 6 hours

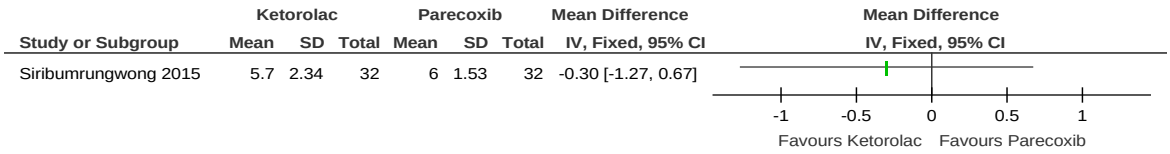


Figure 55: Pain score ≥ 6 – 24 hours

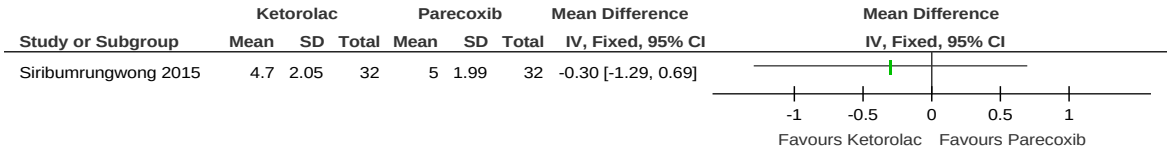


Figure 56: Total pain relief (TOTPAR) 6 hours

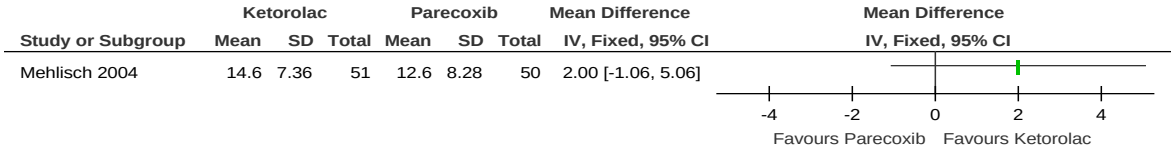


Figure 57: Total pain relief (TOTPAR) 24 hours

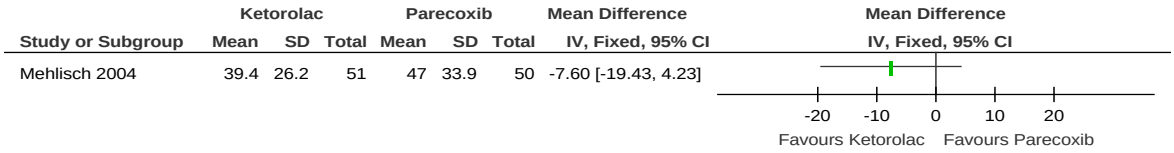


Figure 58: Dose of Opioid ≤ 6 hours

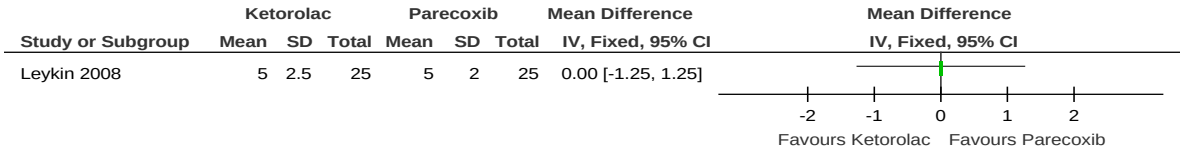


Figure 59: Dose of Opioid ≥ 6 – 24 hours

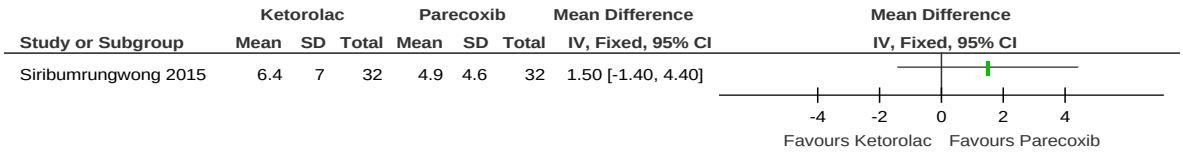
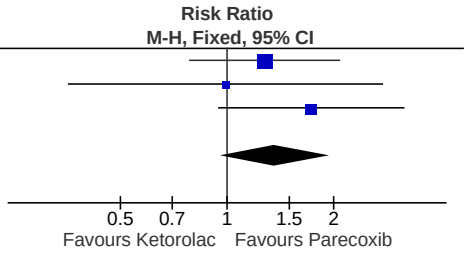


Figure 60: Nausea

Study or Subgroup	Ketorolac Events	Ketorolac Total	Parecoxib Events	Parecoxib Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	17	41	25	77	49.1%	1.28 [0.79, 2.08]
Daniels 2001	5	51	10	101	18.9%	0.99 [0.36, 2.74]
Mehlisch 2003	13	50	23	153	32.0%	1.73 [0.95, 3.15]
Total (95% CI)		**142**		**331**	**100.0%**	**1.37 [0.96, 1.95]**
Total events	35		58			

Heterogeneity: Chi² = 1.05, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.08)

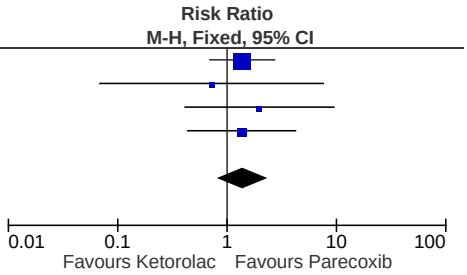


1

Figure 61: Vomiting

Study or Subgroup	Ketorolac Events	Ketorolac Total	Parecoxib Events	Parecoxib Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	11	41	15	77	56.3%	1.38 [0.70, 2.72]
Bikhazi 2004	1	27	2	39	8.8%	0.72 [0.07, 7.57]
Daniels 2001	3	51	3	101	10.9%	1.98 [0.41, 9.47]
Mehlisch 2003	4	50	9	153	24.0%	1.36 [0.44, 4.23]
Total (95% CI)		**169**		**370**	**100.0%**	**1.38 [0.81, 2.35]**
Total events	19		29			

Heterogeneity: Chi² = 0.50, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)

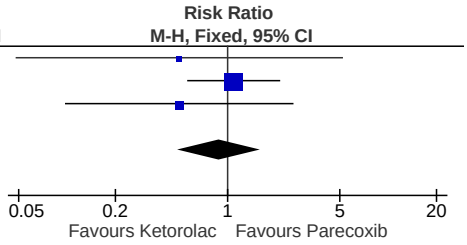


2

Figure 62: Nausea & Vomiting

Study or Subgroup	Ketorolac Events	Ketorolac Total	Parecoxib Events	Parecoxib Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Leykin 2008	1	25	2	25	11.8%	0.50 [0.05, 5.17]
Siribumrungwong 2015	12	32	11	32	64.7%	1.09 [0.57, 2.10]
Wong 2010	2	33	4	33	23.5%	0.50 [0.10, 2.55]
Total (95% CI)		**90**		**90**	**100.0%**	**0.88 [0.49, 1.59]**
Total events	15		17			

Heterogeneity: Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.68)

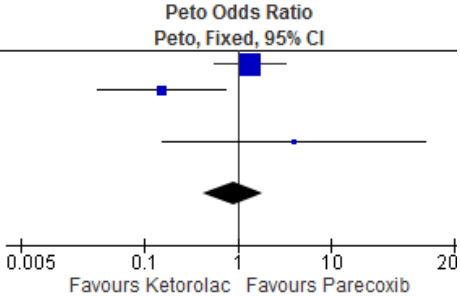


3

Figure 63: Abdominal Pain

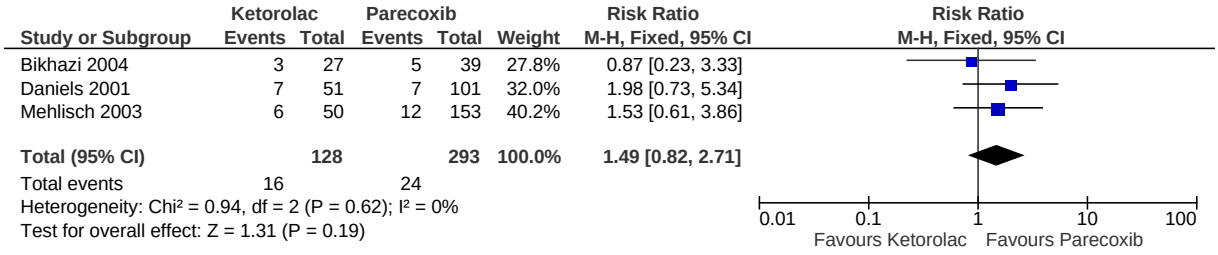
Study or Subgroup	Ketorolac Events	Ketorolac Total	Parecoxib Events	Parecoxib Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Barton 2002	12	41	18	77	72.9%	1.36 [0.57, 3.24]
Bikhazi 2004	0	27	7	39	21.9%	0.15 [0.03, 0.75]
Leykin 2008	0	25	0	25		Not estimable
Mehlisch 2003	1	50	1	153	5.3%	3.95 [0.16, 99.29]
Total (95% CI)		**143**		**294**	**100.0%**	**0.89 [0.43, 1.87]**
Total events	13		26			

Heterogeneity: Chi² = 6.43, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.29 (P = 0.77)



4

Figure 64: Headache



1

Figure 65: Pruritis

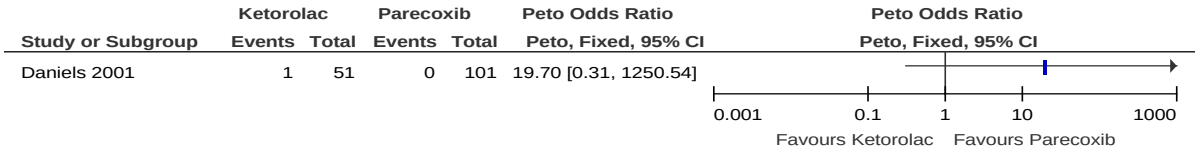
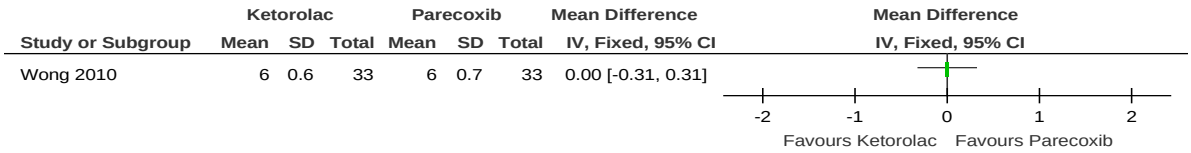


Figure 66: Length of stay



2

D.8 Diclofenac versus Celecoxib

Figure 67: Total pain relief (TOTPAR) 6 hours

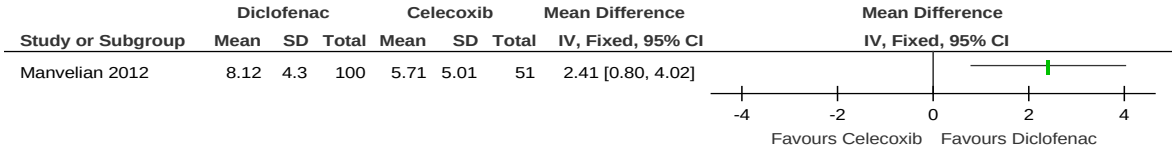


Figure 68: Total pain relief (TOTPAR) 24 hours

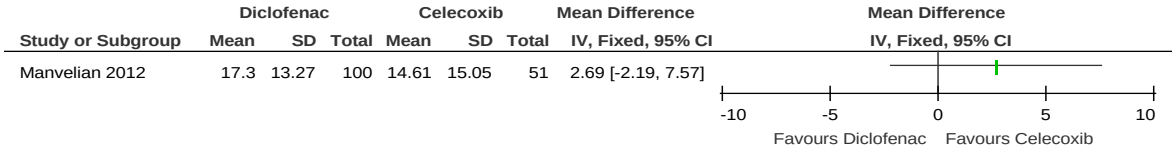


Figure 69: Nausea

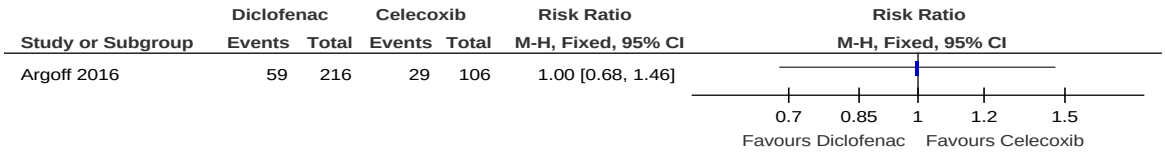


Figure 70: Vomiting

Study or Subgroup	Diclofenac Events	Total	Celecoxib Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Argoff 2016	20	216	15	106	56.6%	0.65 [0.35, 1.23]
Wattchow 2009	20	69	16	74	43.4%	1.34 [0.76, 2.37]
Total (95% CI)		**285**		**180**	**100.0%**	**0.95 [0.63, 1.44]**
Total events	40		31			

Heterogeneity: Chi² = 2.76, df = 1 (P = 0.10); I² = 64%
Test for overall effect: Z = 0.23 (P = 0.82)

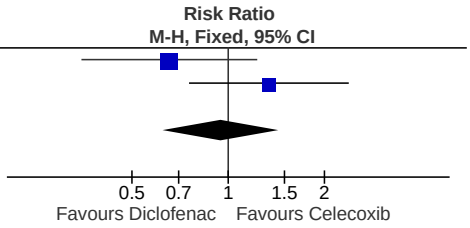


Figure 71: Dizziness

Study or Subgroup	Diclofenac Events	Total	Celecoxib Events	Total	Risk Ratio M-H, Fixed, 95% CI
Argoff 2016	22	216	11	106	0.98 [0.49, 1.95]

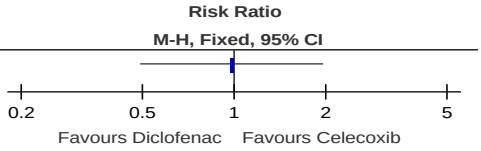


Figure 72: Headache

Study or Subgroup	Diclofenac Events	Total	Celecoxib Events	Total	Risk Ratio M-H, Fixed, 95% CI
Argoff 2016	28	216	11	106	1.25 [0.65, 2.41]

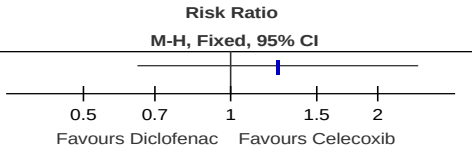
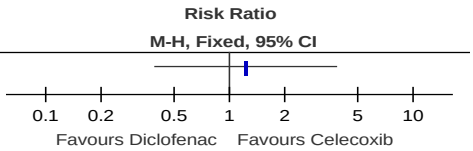


Figure 73: Pruritus

Study or Subgroup	Diclofenac Events	Total	Celecoxib Events	Total	Risk Ratio M-H, Fixed, 95% CI
Argoff 2016	10	216	4	106	1.23 [0.39, 3.82]



D.9 Ibuprofen versus Celecoxib

Figure 74: Pain score ≤ 6 hours

Study or Subgroup	Ibuprofen Mean	SD	Total	Celecoxib Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Akinbade 2018	3.896	2.23	41	3.235	2.396	44	34.6%	0.66 [-0.32, 1.64]
White 2011	2	2	60	2	2	60	65.4%	0.00 [-0.72, 0.72]
Total (95% CI)			**101**			**104**	**100.0%**	**0.23 [-0.35, 0.81]**

Heterogeneity: Chi² = 1.13, df = 1 (P = 0.29); I² = 12%
Test for overall effect: Z = 0.78 (P = 0.44)

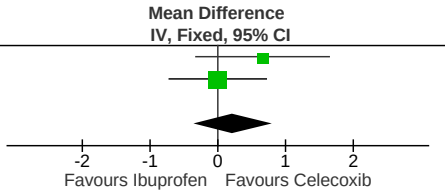


Figure 75: Pain score ≥ 6 – 24 hours

Study or Subgroup	Ibuprofen Mean	SD	Total	Celecoxib Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Akinbade 2018	2.47	2.816	41	1.984	2.179	44	49.9%	0.49 [-0.59, 1.56]
White 2011	5	3	60	5	3	60	50.1%	0.00 [-1.07, 1.07]
Total (95% CI)			**101**			**104**	**100.0%**	**0.24 [-0.52, 1.00]**

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)

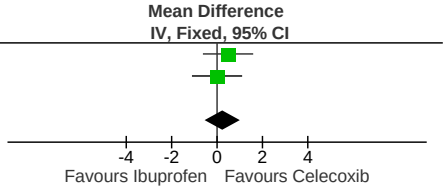
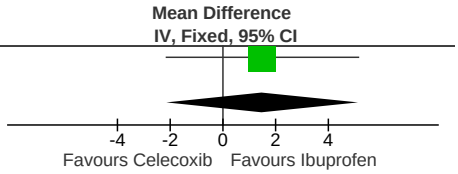


Figure 76: Total pain relief (TOTPAR) 6 hours

Study or Subgroup	Ibuprofen Mean	SD	Total	Celecoxib Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Cheung 2350	14.9	6.2	30	13.4	5.9	16	100.0%	1.50 [-2.14, 5.14]
Total (95% CI)			**30**			**16**	**100.0%**	**1.50 [-2.14, 5.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)



1

Figure 77: Total pain relief (TOTPAR) 6 - 24 hours

Study or Subgroup	Ibuprofen Mean	SD	Total	Celecoxib Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Cheung 2350	38.3	27.8	30	48.8	29.6	16	-10.50 [-28.09, 7.09]

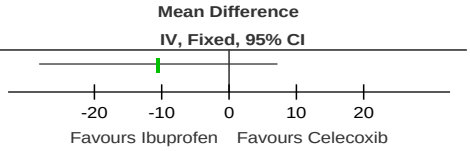
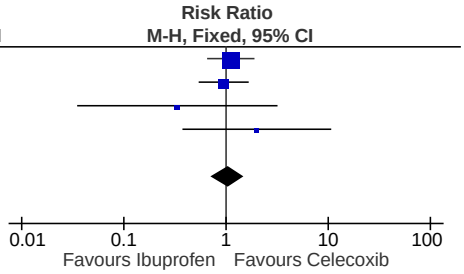


Figure 78: Nausea

Study or Subgroup	Ibuprofen Events	Total	Celecoxib Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Al-Sukhan 2011	27	162	22	147	57.9%	1.11 [0.66, 1.87]
Cheung 2350	16	30	9	16	29.5%	0.95 [0.55, 1.64]
Doyle 2002	1	74	3	74	7.5%	0.33 [0.04, 3.13]
White 2011	4	60	2	60	5.0%	2.00 [0.38, 10.51]
Total (95% CI)		**326**		**297**	**100.0%**	**1.05 [0.72, 1.53]**
Total events	48		36			

Heterogeneity: Chi² = 1.77, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

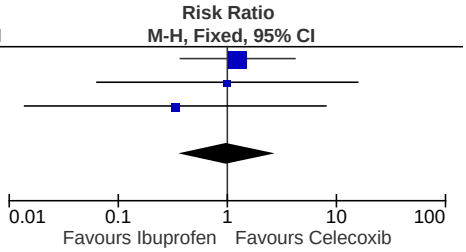


2

Figure 79: Vomiting

Study or Subgroup	Ibuprofen Events	Total	Celecoxib Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cheung 2350	7	30	3	16	61.0%	1.24 [0.37, 4.17]
Doyle 2002	1	74	1	74	15.6%	1.00 [0.06, 15.69]
White 2011	0	60	1	60	23.4%	0.33 [0.01, 8.02]
Total (95% CI)		**164**		**150**	**100.0%**	**0.99 [0.36, 2.77]**
Total events	8		5			

Heterogeneity: Chi² = 0.59, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)

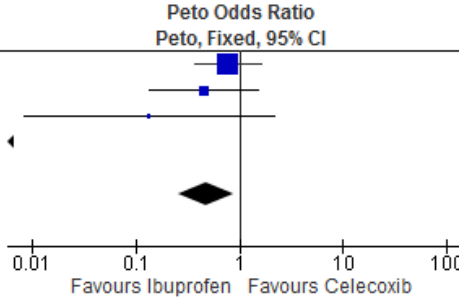


3

Figure 80: Headache

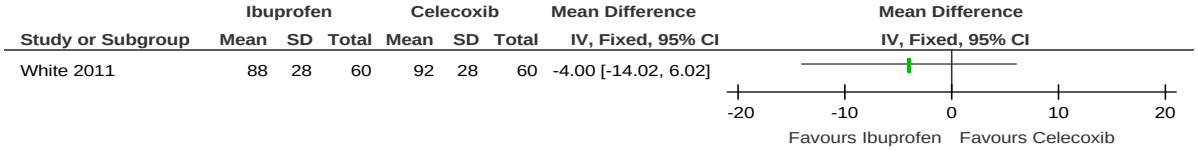
Study or Subgroup	Ibuprofen Events	Total	Celecoxib Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Al-Sukhan 2011	15	162	17	147	68.8%	0.78 [0.38, 1.62]
Cheung 2350	11	30	9	16	25.1%	0.46 [0.14, 1.54]
Doyle 2002	0	74	2	74	4.8%	0.13 [0.01, 2.15]
White 2011	0	60	3	3	1.3%	0.00 [0.00, 0.00]
Total (95% CI)		**326**		**240**	**100.0%**	**0.48 [0.26, 0.88]**
Total events	26		31			

Heterogeneity: Chi² = 60.39, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.38 (P = 0.02)



4

Figure 81: Time to ambulation (minutes)



D.10 Ketorolac versus Celecoxib

Figure 82: Pain score ≥ 6 – 24 hours

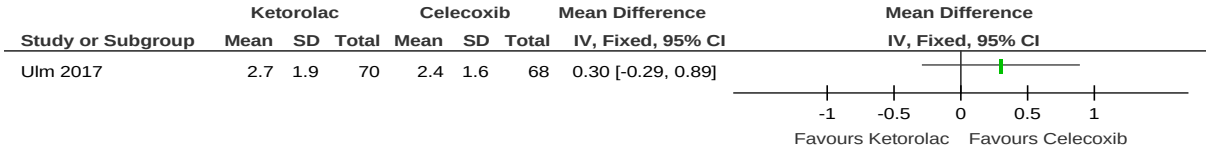
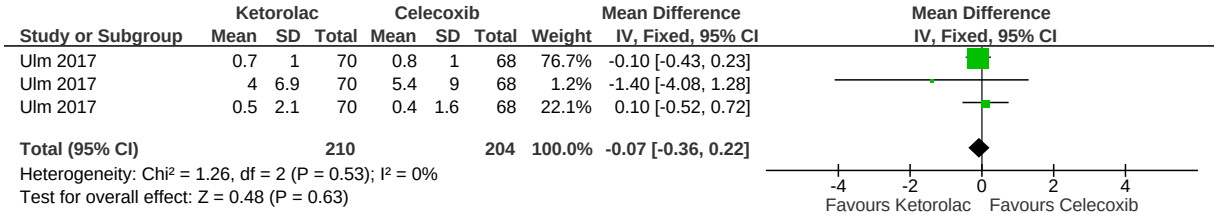


Figure 83: Dose of Opioid ≥ 6 – 24 hours



Appendix E: GRADE tables

Table 10: Risk of bias summary from the overview of Cochrane reviews

Overview review	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Overall risk of bias
Moore 2015[749]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
/Moore 2015[750]	Low concern	Low concern	Low concern	Low concern	Low risk of bias

Table 11: Risk of bias summary from the Cochrane reviews

Systematic review	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Overall risk of bias
Derry 2012[236]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Gaskell 2017[321]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Derry 2015[238]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Wasey 2010[1338]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Tirunagari 2009[1258]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Sultan 2009[1210]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Derry 2009[235]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Moll 2011[740]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Derry 2013[237]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Clarke 2012[190]	Low concern	Low concern	Low concern	Low concern	Low risk of bias
Roy 2010[1075]	Low concern	Low concern	Low concern	Low concern	Low risk of bias

Table 12: Clinical evidence profile: NSAIDs versus placebo

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Placebo	Relative (95% CI)	Absolute		
Participants with at least 50% pain relief over 6 hours												
n/a	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	7720/15603 (49.5%)	15.5%	RR 3.17 (3.04 to 3.30)	336 more per 1000 (from 316 more to 356 more)	⊕⊕⊕O MODERATE	CRITICAL
Participants with at least one adverse event												
n/a	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1851/11560 (16%)	13.7%	RR 1.07 (1.00 to 1.14)	10 more per 1000 (from 0 more to 19 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Participants using rescue medication at 6 hours												
n/a	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	3242/7433 (43.6%)	72.5%	RR 0.6 (0.58 to 0.62)	290 fewer per 1000 (from 275 fewer to 305 fewer)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 13: Clinical evidence profile: COX-2 inhibitors versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	COX-2 inhibitors	Placebo	Relative (95% CI)	Absolute		
Participants with at least 50% pain relief over 6 hours												
n/a	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	866/1759 (49.2%)	9.1%	RR 5.74 (4.66 to 7.07)	431 more per 1000 (from 333 more to 552 more)	⊕⊕OO LOW	CRITICAL
Participants with at least one adverse event												
n/a	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	534/1969 (27.1%)	31.10%	RR 0.92 (0.82 to 1.04)	25 fewer per 1000 (from 56 fewer to 12 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Participants using rescue medication at 6 hours												
n/a	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	684/1117 (61.2%)	90.9%	RR 0.73 (0.69 to 0.76)	245 fewer per 1000 (from 218 fewer to 282 fewer)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by because the point estimate varies widely across studies, I2=50%, p=0.04.

Table 14: Clinical evidence profile: Naproxen versus Ibuprofen

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Naproxen**	**Ibuprofen**	**Relative (95% CI)**	**Absolute**		
TOTPAR 6 hours (follow-up 6 hours; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	161	162	-	MD 1.07 higher (0.72 lower to 2.86 higher)	⊕⊕⊕O MODERATE	CRITICAL
TOTPAR >6-24h hours (Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	161	162	-	MD 3.65 higher (0.13 to 7.17 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain relief (50% resolved) (follow-up 24 hours; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	81	81	-	MD 0 higher (0.11 lower to 0.11 higher)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 15: Clinical evidence profile: Ketorolac versus Diclofenac

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketorolac	Diclofenac	Relative (95% CI)	Absolute		
Pain score ≤6 hours (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	80	80	-	MD 0.09 lower (0.5 lower to 0.33 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain score >6-24 hours (follow-up 24 hours hours; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	25	25	-	MD 0.11 lower (0.39 lower to 0.17 higher)	⊕⊕OO LOW	CRITICAL
Dose of Opioid ≤6 hours (follow-up 6 hours; Better indicated by lower values)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	77	78	-	SMD 0.17 lower (0.49 lower to 0.14 higher)	⊕⊕⊕O MODERATE	CRITICAL
Dose of Opioid 6-24 hours (Better indicated by lower values)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	68	68	-	SMD 0.36 higher (0.1 lower to 0.81 higher)	⊕⊕OO LOW	CRITICAL
Total Pain Relief (TOTPAR6) (follow-up 6 hours; Better indicated by higher values)												
2	randomised trials	serious[2]	very serious[1]	no serious indirectness	serious[3]	none	84	294	-	MD 74.95 higher (35.24 to 114.66 higher)	⊕OOO VERY LOW	CRITICAL

Mortality (Postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	9/2576 (0.35%)	0.2%	RR 1.79 (0.6 to 5.35)	2 more per 1000 (from 1 fewer to 9 more)	⊕⊕OO LOW	CRITICAL
Acute Kidney Injury (follow-up Postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/2576 (0.08%)	0.2%	RR 0.5 (0.09 to 2.72)	1 fewer per 1000 (from 2 fewer to 3 more)	⊕⊕OO LOW	IMPORTANT
Surgical site bleed (follow-up Postoepratively)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	39/2576 (1.5%)	1.4%	RR 1.05 (0.67 to 1.64)	1 more per 1000 (from 5 fewer to 9 more)	⊕⊕OO LOW	IMPORTANT
Gastrointestinal bleed (follow-up Postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/2576 (0%)	0%	RR 0.33 (0.01 to 8.15)	-	⊕⊕OO LOW	IMPORTANT
Allergic reaction (follow-up Postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/2576 (0.12%)	0.1%	RR 1 (0.2 to 4.93)	0 fewer per 1000 (from 1 fewer to 4 more)	⊕⊕OO LOW	IMPORTANT
Nausea (follow-up Postoperative)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	53/194 (27.3%)	32.1%	RR 1.04 (0.78 to 1.39)	13 more per 1000 (from 71 fewer to 125 more)	⊕⊕OO LOW	IMPORTANT

Vomiting (follow-up Postoperative)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	29/194 (14.9%)	10%	RR 1.34 (0.82 to 2.18)	34 more per 1000 (from 18 fewer to 118 more)	⊕⊕⊕O MODERATE	IMPORTANT
Nausea & Vomiting (follow-up Postoperative)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/55 (29.1%)	25.3%	RR 1.23 (0.68 to 2.21)	58 more per 1000 (from 81 fewer to 306 more)	⊕OOO VERY LOW	IMPORTANT
Itching (follow-up stoperative)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	13/144 (9%)	13.7%	RR 0.77 (0.39 to 1.5)	32 fewer per 1000 (from 84 fewer to 68 more)	⊕⊕OO LOW	IMPORTANT
Headache (follow-up Postoeprative)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	14/67 (20.9%)	11.4%	RR 1.84 (0.96 to 3.55)	96 more per 1000 (from 5 fewer to 291 more)	⊕⊕OO LOW	IMPORTANT
Other adverse events (follow-up Postoperative)												
3	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	very serious[3]	none	90/2702 (3.3%)	3.2%	RR 0.83 (0.24 to 2.82)	5 fewer per 1000 (from 24 fewer to 58 more)	⊕OOO VERY LOW	IMPORTANT
Length of stay (hours) (follow-up Postoperative; Better indicated by lower values)												
1	randomised	no serious	no serious	no serious	serious[3]	none	50	50	-	MD 2 lower (12.58	⊕⊕⊕O	IMPORTANT

	trials	risk of bias	inconsistency	indirectness						lower to 8.58 higher)	MODERATE	

[1] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 16: Clinical evidence profile: Diclofenac versus Ibuprofen

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diclofenac**	**Ibuprofen**	**Relative (95% CI)**	**Absolute**		
Pain score ≤6 hours (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83	80	-	MD 0.06 higher (0.72 lower to 0.84 higher)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 17: Clinical evidence profile: Ibuprofen versus Ketorolac

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Ketorolac**	**Relative (95% CI)**	**Absolute**		
Dose of Opioid <6 hours (Better indicated by lower values)												
1	randomised	no serious risk	no serious	no serious	no serious	none	20	31	-	MD 14.39 lower (20.47	⊕⊕⊕⊕	CRITICAL

	trials	of bias	inconsistency	indirectness	imprecision					to 8.31 lower)	HIGH	

Table 18: Clinical evidence profile: Ketorolac versus Parecoxib

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketorolac**	**Parecoxib**	**Relative (95% CI)**	**Absolute**		
Pain score <6 hours (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 0.3 lower (1.27 lower to 0.67 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain score 6-24 hours (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 0.3 lower (1.29 lower to 0.69 higher)	⊕⊕⊕O MODERATE	CRITICAL
TOTPAR 6 hours (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	51	50	-	MD 2 higher (1.06 lower to 5.06 higher)	⊕⊕⊕O MODERATE	CRITICAL
TOTPAR 24hours (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	51	50	-	MD 7.6 lower (19.43 lower to 4.23 higher)	⊕⊕⊕O MODERATE	CRITICAL
Dose of Opioid ≤ 6 hours (Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	25	25	-	MD 0 higher (1.25 lower to 1.25 higher)	⊕⊕OO LOW	CRITICAL
Dose of Opioid 6 - 24 hours (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 1.5 higher (1.4 lower to 4.4 higher)	⊕⊕⊕O MODERATE	CRITICAL
Nausea (follow-up Postoperative)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	35/142 (24.6%)	15%	RR 1.37 (0.96 to 1.95)	56 more per 1000 (from 6 fewer to 143 more)	⊕⊕⊕O MODERATE	IMPORTANT
Vomiting (follow-up Postoperative)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	19/169 (11.2%)	5.5%	RR 1.38 (0.81 to 2.35)	21 more per 1000 (from 10 fewer to 74 more)	⊕OOO VERY LOW	IMPORTANT
Nausea & Vomiting (follow-up Postoperative)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	15/90 (16.7%)	12.1%	RR 0.88 (0.49 to 1.59)	15 fewer per 1000 (from 62 fewer to 71 more)	⊕⊕OO LOW	IMPORTANT
Abdominal Pain (follow-up Postoperative)												
4	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[1]	none	13/143 (9.1%)	9.3%	Peto odds 0.89 (0.43 to 1.87)	10 fewer per 1000 (from 53 fewer to 81 more)	⊕OOO VERY LOW	IMPORTANT

Headache (follow-up Postoperative)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	16/128 (12.5%)	7.8%	RR 1.49 (0.82 to 2.71)	38 more per 1000 (from 14 fewer to 133 more)	⊕OOO VERY LOW	IMPORTANT
Pruritis (follow-up Postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/51 (2%)	0%	Peto odds 19.7 (0.31 to 1250.54)	-	⊕⊕⊕O MODERATE	IMPORTANT
Length of stay (follow-up Postoperative; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	33	-	MD 0 higher (0.31 lower to 0.31 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 19: Clinical evidence profile: Diclofenac versus Celecoxib

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diclofenac**	**Celecoxib**	**Relative (95% CI)**	**Absolute**		
TOTPAR 6 hours (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	100	51	-	MD 2.41 higher (0.8 to 4.02 higher)	⊕⊕OO LOW	CRITICAL

TOTPAR 6-24 hours (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	100	51	-	MD 2.69 higher (2.19 lower to 7.57 higher)	⊕⊕OO LOW	CRITICAL
Nausea (follow-up Postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	59/216 (27.3%)	27.4%	RR 1 (0.68 to 1.46)	0 fewer per 1000 (from 88 fewer to 126 more)	⊕⊕OO LOW	IMPORTANT
Vomiting (follow-up Postoperative)												
2	randomised trials	serious[1]	very serious[3]	no serious indirectness	very serious[2]	none	40/285 (14%)	17.9%	RR 0.95 (0.63 to 1.44)	9 fewer per 1000 (from 66 fewer to 79 more)	⊕OOO VERY LOW	IMPORTANT
Dizziness (follow-up postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	22/216 (10.2%)	10.4%	RR 0.98 (0.49 to 1.95)	2 fewer per 1000 (from 53 fewer to 99 more)	⊕⊕OO LOW	IMPORTANT
Headache (follow-up postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	28/216 (13%)	10.4%	RR 1.25 (0.65 to 2.41)	26 more per 1000 (from 36 fewer to 147 more)	⊕⊕OO LOW	IMPORTANT
Pruritis (follow-up postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/216 (4.6%)	3.8%	RR 1.23 (0.39 to 3.82)	9 more per 1000 (from 23 fewer to 107 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 20: Clinical evidence profile: Ibuprofen versus Celecoxib

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Celecoxib	Relative (95% CI)	Absolute		
Pain score ≤6 hours (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	101	104	-	MD 0.23 higher (0.35 lower to 0.81 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Pain score 6-24 hours (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	101	104	-	MD 0.24 higher (0.52 lower to 1 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
TOTPAR (6 hours) (Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	30	16	-	MD 1.5 higher (2.14 lower to 5.14 higher)	⊕OOO VERY LOW	CRITICAL
TOTPAR (24 hours) (Better indicated by higher values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	30	16	-	MD 10.5 lower (28.09 lower to 7.09 higher)	⊕OOO VERY LOW	CRITICAL
Nausea (follow-up postoeprative)												

4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	48/326 (14.7%)	9.5%	RR 1.05 (0.72 to 1.53)	5 more per 1000 (from 27 fewer to 50 more)	⊕⊕OO LOW	IMPORTANT
Vomiting (follow-up postoperative)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	8/164 (4.9%)	1.7%	RR 0.99 (0.36 to 2.77)	0 fewer per 1000 (from 11 fewer to 30 more)	⊕OOO VERY LOW	IMPORTANT
Headache (follow-up postoperative)												
4	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[1]	none	26/326 (8%)	33.9%	Peto OR 0.48 (0.26 to 0.88)	176 fewer per 1000 (from 41 fewer to 251 fewer)	⊕OOO VERY LOW	IMPORTANT
Time to ambulation (minutes) (follow-up postoperative; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	60	60	-	MD 4 lower (14.02 lower to 6.02 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 21: Clinical evidence profile: Ketorolac versus Celecoxib

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ketorolac**	**Celecoxib**	**Relative (95% CI)**	**Absolute**		

Pain score 6 - 24 hours (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	70	68	-	MD 0.3 higher (0.29 lower to 0.89 higher)	⊕⊕OO LOW	CRITICAL
Dose of Opioid 6 - 24h (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	210	204	-	MD 0.07 lower (0.36 lower to 0.22 higher)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix F:Health economic evidence tables

None.

Appendix G: Excluded studies

G.1 Excluded clinical studies

Table 22: Studies excluded from the health economic review

Study	Exclusion reason
Ahlstrom 1993[16]	No relevant outcomes
Alanoglu 2005[25]	Incorrect comparison – different modes of administration
Albuquerque 2017[28]	Incorrect comparison – Etoricoxib
Arnold 1990[49]	Incorrect comparison – Ketoprofen
Arponrat 2015[50]	Incorrect comparison
Aziz 2003[63]	No useable outcomes
Barden 2003[75]	Incorrect comparison
Bauduin 1995[86]	Incorrect population – healthy volunteers
Bell 2018[96]	Systematic review – references screened
Boonriong 2010[118]	Incorrect comparison – Etoricoxib
Brown 1997[132]	Incorrect study design – crossover trial
Brown 2013[133]	Incorrect comparison – Etoricoxib
Cheng 2004[166]	Incorrect comparison
Collins 1998[196]	Incorrect comparison
Cooper 1988[203]	Incorrect comparison – Ketoprofen
Daniels 2013[217]	No relevant outcomes
Daniels 2011[218]	Incorrect comparison – Etoricoxib
Dordoni 1994[251]	Incorrect comparison – Ketoprofen
Ekman 2006[265]	Incorrect comparison
Elliott 1993[270]	Incorrect study design – abstract only
Essex 2018[281]	Incorrect comparison
Esteller-Martinez 2004[284]	No relevant outcomes
Facchinetti 2005[287]	Incorrect comparison – Ketoprofen
Fineschi 1997[294]	Incorrect comparison – different modes of administration
Forbes 1992[299]	Incorrect comparison – Bromfenac
Forbes 1991[300]	Incorrect comparison – Bromfenac
Frame 1986[304]	Incorrect comparison – Flurbiprofen
Gallardo 1981[313]	No relevant outcomes
Gallardo 1980[314]	No relevant outcomes
Gan 2017[316]	No relevant outcomes
Gan 2016[317]	No relevant outcomes
Gazal 2017[322]	Incorrect population – under 18 included
Gimbel 2001[334]	Incorrect comparison
Graf 2008[344]	No relevant outcomes
Gupta 1997[360]	Incorrect comparison – Flurbiprofen
Gurunathan 2016[363]	Incorrect comparison
Hanna 2019[379]	Systematic review – references screened; incorrect comparison
Hanzawa 2018[382]	No relevant outcomes
Higgins 1994[397]	Incorrect comparison – different modes of administration

Study	Exclusion reason
Hynninen 2000[425]	Incorrect comparison – Ketoprofen
Inthigood 2017[429]	Incorrect comparison
Ishiguro 2015[430]	Incorrect comparison – Etodolac
Isola 2019[431]	No relevant outcomes
Issioui 2002[432]	Incorrect comparison
Johnson 1997[455]	Incorrect comparison – Bromfenac
Kahlenberg 2017[471]	Incorrect comparison
Karaman 2006[486]	Incorrect comparison – Lornoxicam / Ketorprofen
Karst 2003[492]	Incorrect comparison
Kellstein 2004[499]	Incorrect intervention – one study drug
Khan 2002[504]	No relevant outcomes
Kim 2009[513]	Incorrect comparison
Kuang 2016[555]	Incorrect comparison
Laveneziana 1996[576]	Incorrect comparison – different modes of administration
Lee 2004[591]	Incorrect comparison
Lee 2007[581]	Systematic review – references screened
Lenz 2008[597]	Incorrect comparison – Etoricoxib
Lierz 2012[614]	Incorrect comparison – Etoricoxib
Lionberger 2005[619]	Incorrect comparison
Liu 2005[627]	Incorrect comparison – Etoricoxib
Liu 2016[629]	Incorrect comparison
Luscombe 2010[644]	Incorrect comparison
Macario 2001[647]	Incorrect comparison
Malan 2003[656]	Incorrect comparison – Indomethacin
Malmstrom 2004[658]	Incorrect comparison – Etoricoxib
Manyou 2008[665]	Incorrect comparison – Etoricoxib
Mardani-Kivi 2013[669]	Incorrect comparison
Martinez 2007[674]	Incorrect comparison
Matsota 2013[682]	Incorrect comparison
McNicol 2018[693]	Systematic review – references screened
Meunier 2007[715]	Incorrect comparison
Mizraji 1990[732]	Incorrect comparison
Mu 2017[772]	Incorrect comparison
Munteanu 2016[775]	Incorrect comparison - Etoricoxib
Murthy 2012[780]	Incorrect comparison – Lornoxicam
Nalini 2017[786]	Incorrect comparison – Lornoxicam
Ng 2017[913]	Incorrect comparison
Ng 2008[911]	Incorrect comparison – different modes of administration
Ng 2003[910]	Incorrect comparison
Niemi 1995[921]	Incorrect comparison – Ketoprofen
Nishina 2000[925]	Incorrect comparison – Flurbiprofen
Oh 2018[933]	No relevant outcomes
Olmedo 2001[939]	Incorrect comparison – Ketoprofen
Olson 2001[940]	Incorrect comparison – Ketoprofen
Pagnoni 1996[958]	Incorrect comparison – different modes of administration

Study	Exclusion reason
Papadima 2007[969]	Incorrect comparison – Lornoxicam
Pareek 2011[972]	Incorrect comparison – Etodolac
Parsa 2005[986]	Incorrect comparison
Patrocinio 2007[989]	Incorrect comparison – Ketoprofen
Phinchantra 2004[1004]	Incorrect comparison
Phittayawechwiwat 2007[1005]	Incorrect comparison – Etoricoxib
Polat 2005[1008]	Incorrect population – under 18 included
Puolakka 2006[1019]	Incorrect comparison
Puura 2006[1020]	Incorrect comparison – Etoricoxib
Rasmussen 2005[1038]	Incorrect comparison – Etoricoxib
Ratchanon 2011[1040]	Incorrect comparison
Rawal 2013[1047]	Incorrect comparison – Etoricoxib
Recart 2003[1048]	Incorrect comparison
Renner 2010[1051]	Incorrect comparison – Etoricoxib
Reuben 2008[1052]	Incorrect comparison
Reuben 2005[1053]	Incorrect comparison
Reuben 2007[1054]	Incorrect comparison
Roelofse 1996[1066]	Incorrect comparison – Tenoxicam
Roelofse 1993[1065]	Incorrect comparison – Tenoxicam
Rorarius 1993[1068]	Incorrect comparison – Ketoprofen
Rowe 1981[1074]	Incorrect comparison – Mefenamic acid
Sacchetti 1978[1084]	Incorrect comparison – Indoprofen
Saito 2012[1093]	Incorrect comparison
Sandhu 2011[1099]	Incorrect comparison – Etoricoxib
Sarridou 2015[1104]	Incorrect comparison
Scott 1986[1118]	Incorrect comparison – Etodolac / Zomepirac
Sehgal 2003[1120]	Incorrect comparison – Ketoprofen
Sekiguchi 2015[1122]	Incorrect comparison – Loxoprofen
Senard 2010[1126]	Incorrect comparison
Sener 2005[1127]	Incorrect comparison – Diflusinal / Meloxicam / Rofecoxib
Sener 2008[1128]	Incorrect comparison – Lornoxicam / Ketoprofen
Seymour 2000[1132]	Incorrect comparison – Ketoprofen
Siddiqui 2008[1140]	Incorrect comparison – Etoricoxib
Silva de Oliveira 2016[1145]	Incorrect comparison – Etodolac
Silvanto 2002[1147]	Incorrect comparison – Ketoprofen
Smirnov 2008[1171]	Incorrect comparison – Etoricoxib
Somri 2017[1179]	Incorrect comparison – Etoricoxib
Srivastava 2012[1187]	Incorrect comparison – Etoricoxib
Tai 1992[1228]	Incorrect comparison – Ketoprofen
Tang 2002[1239]	Incorrect comparison
Toivonen 2007[1261]	Incorrect comparison – Etoricoxib
Toshiko Hirahara 2003[1263]	Incorrect comparison – Ketoprofen
Tuzuner Oncul 2011[1280]	Incorrect comparison – Lornoxicam
Vaidya 1974[1295]	Incorrect comparison – Mefenamic acid
Van Daele 2016[1298]	Incorrect comparison

Study	Exclusion reason
van Helmond 2016[1306]	Incorrect comparison
Vasigh 2016[1309]	Incorrect comparison
Verma 2015[1311]	Incorrect comparison – Lornoxicam
Viscusi 2012[1317]	Incorrect comparison – Etoricoxib
Viscusi 2008[1318]	Incorrect comparison
Watcha 2003[1341]	Incorrect comparison
White 2007[1353]	Incorrect comparison
Yamashita 2006[1383]	Incorrect comparison – Loxoprofen
Zhang 2014[1437]	Incorrect comparison
Zhao 2011[1438]	Incorrect comparison
Zhu 2018[1442]	Incorrect comparison
Zhu 2016[1443]	Incorrect comparison
Zittel 2013[1444]	Incorrect comparison – Etoricoxib

G.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 23: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Opioid

Appendix A: Review protocol

Table 24: Review protocol: Managing acute postoperative pain: IV versus oral opioid

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	What is the most clinically and cost effective strategy for managing acute postoperative pain?
2.	Review question	What is the most clinically and cost effective strategy for managing acute postoperative pain? There are six topic areas that have been identified: Paracetamol routes of delivery Non-steroidal anti-inflammatory drugs (NSAIDs) Opioid administration strategy (Continuous epidural ,intravenous PCA, spinal) Opioid post-operative administration strategy (oral vs iv) Ketamine Neuropathic nerve stabilisers This protocol addresses, 'What is the clinical and cost effectiveness of IV opioid compared to oral opioid given post operatively in managing acute post operative pain?'
3.	Objective	To determine the most clinically and cost effective opioid strategy given post operatvely in managing acute post operative pain.
4.	Searches	The following databases will be searched: • Embase • MEDLINE • The Cochrane Library Searches will be restricted by: • English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being	What is the most clinically and cost effective

	studied	strategy for managing acute postoperative pain
6.	Population	Inclusion: Adults (18 years and older) who have undergone surgery. Exclusion: People who have had Surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	Interventions: • PCA • Oral Opioid (immediate release) • Oral opioid (modified release)
8.	Comparator/Reference standard/Confounding factors	Comparators: • Each other
9.	Types of study to be included	Randomised controlled trials and systematic reviews of randomised controlled trials
10.	Other exclusion criteria	Non-English language Cross-over randomised controlled trials
11.	Context	NA

12.	Primary outcomes (critical outcomes)	• Health-related quality of life
		• Pain reduction
		  ○ < 6 hours post op
		  ○ 6 hours- 24 hours post op
		Pain reduction measured by:
		• patient reported pain (physician, nurse or carer reported pain will not be included);
		• patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both)
		• patient reported pain intensity expressed hourly over four to six hours using validated pain scales, or reported summed pain intensity difference (SPID) at four to six hours
		• Number of participants achieving at least 50% pain relief
		• Time to achieve 50% pain intensity
		• Amount of additional medication use (rescue medication)
		  ○ < 6 hours post op
		  ○ 6 hours- 24 hours post op
		• Time to rescue medication
		• Adverse events (including respiratory depression, nausea, vomiting)

13.	Secondary outcomes (important outcomes)	• Psychological distress and mental well-being • Symptom scores

		• Functional measures • Length of stay in intensive care • Length of stay in hospital • Hospital readmission The committee agreed that a difference of 1 (10%) on a 10 point pain scale such as NRS or VRS indicated a clinically important difference. For the remaining outcomes, the committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Cochrane RoB (2.0) will be used to assess intervention reviews 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management The clinical approach to this area of the scope is multimodal. The pain management approach

		for each patient will depend on many factors and include the procedure and the severity of pain. For this reason it is not meaningful to compare the drugs listed in the topic areas to each other. There isn't an overall question evaluating which drug is the most effective and a network meta-analysis is not appropriate.	
17.	Analysis of sub-groups	Subgroups: • people aged over 60 years • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation • American Society of Anesthesiologists (ASA) Physical Status grade	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	NA	
22.	Anticipated completion date	NA	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☑
		Piloting of the study selection process	☐ / ☑
		Formal screening of search results against eligibility criteria	☐ / ☑
		Data extraction	☐ / ☑
		Risk of bias (quality) assessment	☐ / ☑
		Data analysis	☐ / ☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail	

		perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swaine Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis Ms Lina Gulhane
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	NA

30.	Reference/URL for published protocol	NA	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • Issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Perioperative care Pain relief Paracetamol	
33.	Details of existing review of same topic by same authors	NA	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	NA	
36.	Details of final publication	www.nice.org.uk	

Table 25: Review protocol: Managing acute postoperative pain: opioid administration strategy

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	What is the most clinically and cost effective strategy for managing acute postoperative pain?
2.	Review question	What is the most clinically and cost effective strategy for managing acute postoperative pain? There are six topic areas that have been identified: Paracetamol routes of delivery Non-steroidal anti-inflammatory drugs (NSAIDs) Opioid administration strategy (Continuous epidural ,intravenous PCA, spinal)

		Opioid post-operative administration strategy (oral vs iv) Ketamine Neuropathic nerve stabilisers This protocol addresses, 'What is the most clinically and cost effective opioid administration strategy ?'
3.	Objective	To determine the most clinically and cost effective opioid strategy given post operatvely in managing acute post operative pain.
4.	Searches	The following databases will be searched: • Embase • MEDLINE • The Cochrane Library Searches will be restricted by: • English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	What is the most clinically and cost effective strategy for managing acute postoperative pain
6.	Population	Inclusion: Adults (18 years and older) who have undergone surgery. Exclusion: People who have had Surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	Interventions: • IV PCA (morphine, fentanyl,oxycodone) • Spinal opioid – one administration (diamporphine or/morphine +/- bupivacaine/ levobupivacaine • Continuous epidural (Fentanyl + Bupivacaine, Morphine + bupivacaine)
8.	Comparator/Reference standard/Confounding factors	Comparators: • Each other
9.	Types of study to be included	Randomised controlled trials and systematic reviews of randomised controlled trials
10.	Other exclusion criteria	Non-English language Cross-over randomised controlled trials
11.	Context	NA

12.	Primary outcomes (critical outcomes)	• Health-related quality of life
		• Pain reduction
		  ○ < 6 hours post op
		  ○ 6 hours- 24 hours post op
		Pain reduction measured by:
		• patient reported pain (physician, nurse or carer reported pain will not be included);
		• patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both)
		• patient reported pain intensity expressed hourly over four to six hours using validated pain scales, or reported summed pain intensity difference (SPID) at four to six hours
		• Number of participants achieving at least 50% pain relief
		• Time to achieve 50% pain intensity
		• Amount of additional medication use (rescue medication)
		  ○ < 6 hours post op
		  ○ 6 hours- 24 hours post op
		• Time to rescue medication
		• Adverse events (including respiratory depression, nausea, vomiting)

13.	Secondary outcomes (important outcomes)	• Psychological distress and mental well-being • Symptom scores • Functional measures • Length of stay in intensive care • Length of stay in hospital • Hospital readmission The committee agreed that a difference of 1 (10%) on a 10 point pain scale such as NRS or VRS indicated a clinically important difference. For the remaining outcomes, the committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be

		retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.	
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Cochrane RoB (2.0) will be used to assess intervention reviews 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management The clinical approach to this area of the scope is multimodal. The pain management approach for each patient will depend on many factors and include the procedure and the severity of pain. For this reason it is not meaningful to compare the drugs listed in the topic areas to each other. There isn't an overall question evaluating which drug is the most effective and a network meta-analysis is not appropriate.	
17.	Analysis of sub-groups	Subgroups: • people aged over 60 years • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation • American Society of Anesthesiologists (ASA) Physical Status grade	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic

<table>
<tr><td></td><td></td><td>☐</td><td>Service Delivery</td></tr>
<tr><td></td><td></td><td>☐</td><td>Other (please specify)</td></tr>
<tr><td>19.</td><td>Language</td><td colspan="2">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="2">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="2">NA</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="2">NA</td></tr>
<tr><td>23.</td><td>Stage of review at time of this submission</td><td colspan="2"><table>
<tr><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☑</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☑</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☑</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☑</td></tr>
</table></td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="2">5a. Named contact
National Guideline Centre

5b Named contact e-mail
perioperativecare@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and the National Guideline Centre</td></tr>
<tr><td>25.</td><td>Review team members</td><td colspan="2">From the National Guideline Centre:
Ms Sharon Swain – Guideline lead
Ms Kate Kelley – Guideline lead
Mr Ben Mayer – Senior systematic reviewer
Ms Maria Smyth – Senior systematic reviewer
Mr Audrius Stonkus – Systematic reviewer
Mr Vimal Bedia – Systematic reviewer
Ms Madelaine Zucker – Systematic reviewer</td></tr>
</table>

		• Ms Margaret Constanti – Senior Health economist • Ms Annabelle Davies – Health economist • Ms Lina Gulhane – Information specialist • Ms Kate Ashmore – Project manager
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	NA
30.	Reference/URL for published protocol	NA
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • Issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Perioperative care Pain relief Paracetamol
33.	Details of existing review of same	NA

	topic by same authors		
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	NA	
36.	Details of final publication	www.nice.org.uk	

The health economic review protocol is shown in Table **3**.

Appendix B: Clinical evidence selection

Figure 84: Flow chart of clinical study selection for the review of IV opioid versus oral opioid

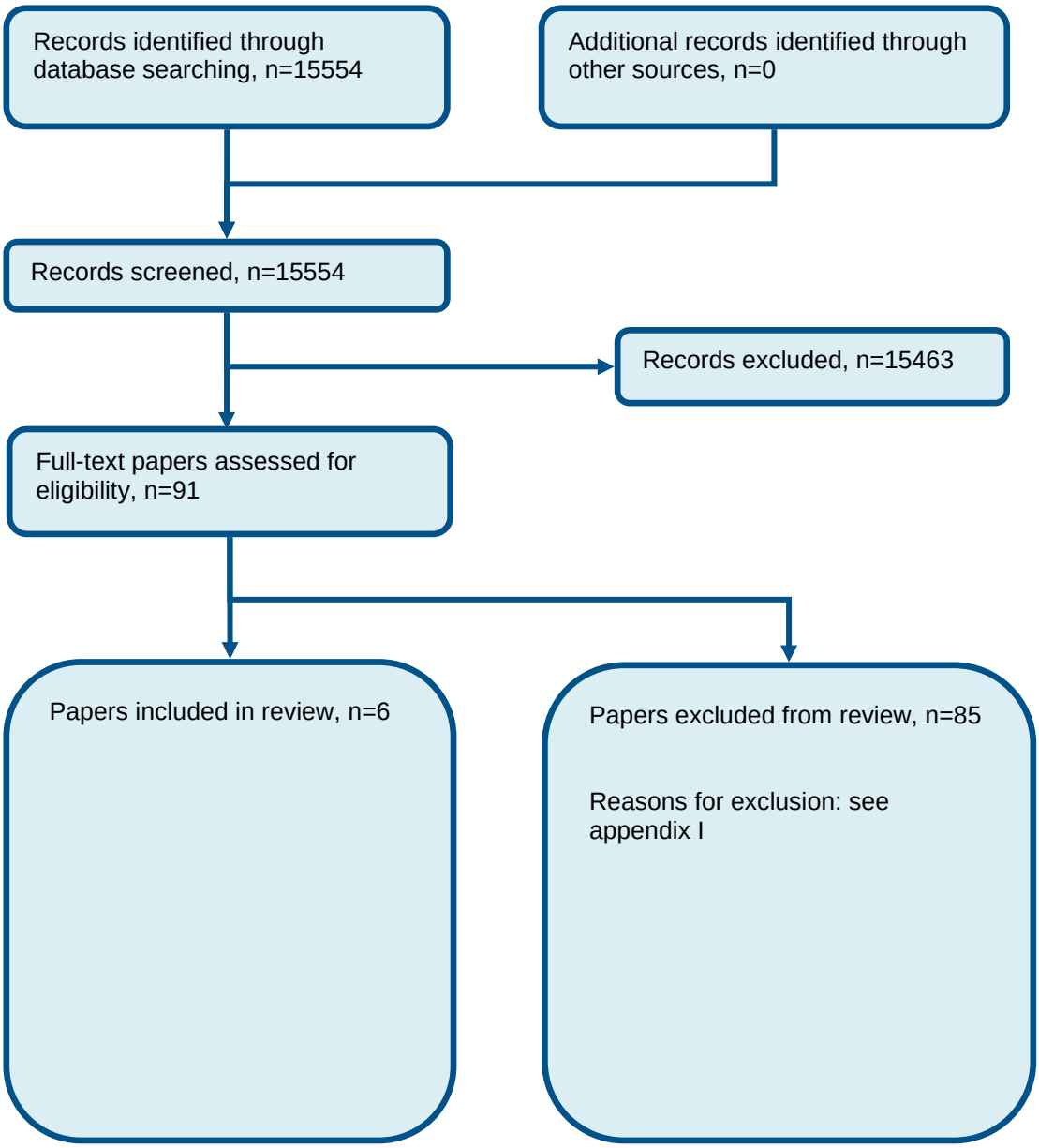
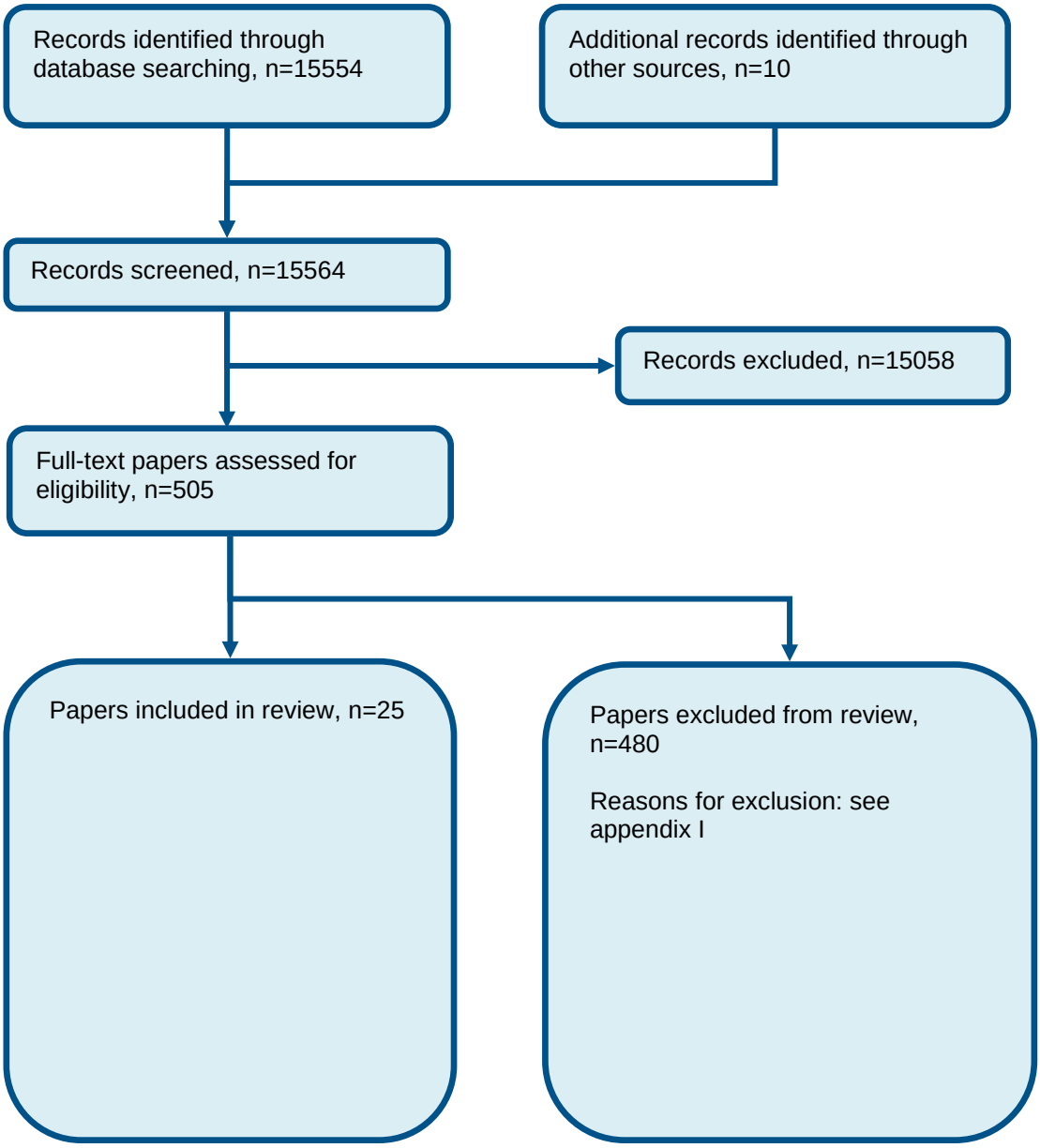


Figure 85: Flow chart of clinical study selection for the review of opioid administration strategy



1
2

Appendix C: Clinical evidence tables

Study	Ruetzler 2014[1080]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=51)
Countries and setting	Conducted in Austria; Setting: department of cardiothoracic and vascular anaesthesia and intensive care
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	51 patients scheduled for elective conventional on-pump cardiac surgery requiring median sternotomy between July 2011 and May 2012
Exclusion criteria	Exclusion criteria were chronic use of opioids, tranquilizers or pain medications within 3 months; hypersensitivity to opioids; use of monoamine oxidase inhibitors in the 2 weeks before surgery; alcohol or drug abuse; renal dysfunction defined as Child-Pugh score 7-15; ejection fraction of <40%; malabsorbsion syndrome; neurologic or cognitive dysfunction; pregnancy; severe respiratory depression; severe obstructive pulmonary disease; severe bronchial asthma; non-opioid induced paralytic ileus; history of seisures.
Recruitment/selection of patients	not satated
Age, gender and ethnicity	Age - Mean (SD): IV 63(14); Oral 67(15). Gender (M:F): 41/10. Ethnicity: NA not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 4 (3 and 4). 3. Type of surgery: vascular (cardiac surgery).
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: PCA - IV patient controlled analgesia. Patients assigned to PCA were given a basal rate of 0.3 mg morphine per hour. Demand dose was a 1 mg bolus with a 5 min lockout, but no other hourly limit.. Duration not stated. Concurrent medication/care: Patients were premedicated with 7.5 mg midazolam. General anaesthesia was induced with fentanyl and approximately 3µg/kg, propofol at approximately 1.5mg/kg and rucoronium at approximately 0.6 mg/kg. General anaesthesia was maintained with sevoflurane combined with 0.2-04 µg/kg/min remifentanil as clinically neccesary. at 30 min before anticipated end of surgery, patients were given 1 g paracetamol IV. At the end of the surgery, patients were transfered to the ICU, still intubated and ventilated, and remifentanil was reduced to 0.05 µg/kg/min. Remifentanil was

Study	Ruetzler 2014[1080]
	discontinued 3 h after surgery. patients were thereafter given 1 g paracetamol IV at 6-h intervals throughout the first 3 post operative days.. Indirectness: No indirectness (n=25) Intervention 2: Oral Opioid - Modified release. Patients assigned to oral group were given 20 mg Targin tablets at 12 h intervals, corresponding to a daily dose of 36 mg oxycodone. On their demand or when VAS exceeded 30 mm, patients were given an additional 5 mg oxycodone hydrochloride which was repeated as necessary at 30 min intervals.. Duration not stated. Concurrent medication/care: Patients were premedicated with 7.5 mg midazolam. General anaesthesia was induced with fentanyl and approximately 3µg/kg, propofol at approximately 1.5mg/kg and rucoronium at approximately 0.6 mg/kg. General anaesthesia was maintained with sevoflurane combined with 0.2-04 µg/kg/min remifentanil as clinically neccesary. at 30 min before anticipated end of surgery, patients were given 1 g paracetamol IV. At the end of the surgery, patients were transfered to the ICU, still intubated and ventilated, and remifentanil was reduced to 0.05 µg/kg/min. Remifentanil was discontinued 3 h after surgery. patients were thereafter given 1 g paracetamol IV at 6-h intervals throughout the first 3 post operative days.. Indirectness: No indirectness
Funding	Other (funded by internal sources only)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PATIENT CONTROLLED ANALGESIA versus MODIFIED RELEASE

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: VAS score reported as adjusted difference of means at postoperatively; VAS score reported as adjusted difference of means oral vs IV 3.44 (-4.29; 11.17);
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Adverse events (Nausea +vomiting) at 3 days postoperatively; Group 1: 11/26, Group 2: 8/24
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 3: Length of stay in intensive care unit
- Actual outcome: length of stay at ICU at postoperatively; Length of stay at ICU reported as median(1st quartile, 3rd quartile) was 1 (1,2) days for both groups;
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Study	Ruetzler 2014[1080]
Protocol outcome 4: Length of hospital stay - Actual outcome: LOS at postoperatively; Length of hospital stay was reported as median was 8.5 (8, 12) days for oral group and 9 (8, 11) for the PCA group.; Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Hospital readmission

Study	Davis 2006[222]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=93)
Countries and setting	Conducted in USA; Setting: the study was carried out at at a New England tertiary care center.
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	all patients aged=>18 years in Labor and Delivery for planned cesarean delivery were offered participation.
Exclusion criteria	unplanned cesarean delivery; a known allergy/ hypersensitivity to morphine, oxycodone or acetaminophen; treatment with magnesium sulfate; the chronic use of narcotics or substance abuse; the use of general anesthesia; or history of a pain syndrome
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): PCA 31.5 (4.7); oral 31.9 (4.5). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (cesarean delivery).
Indirectness of population	No indirectness

Study	Davis 2006[222]
Interventions	(n=47) Intervention 1: PCA - IV patient controlled analgesia. Patients received IV PCA device with preservative free morphine sulfate with a continuous infusion 1 mg/ hr. an additional 1-mg dose was administered on patient demand, with a lockout interval of 6 minutes. After12 hours the PCA was discontinued and oral analgesia was begun with oxycodone-acetaminophen (5/325 mg), with to 2 tablets permitted every 4 hours as needed for pain.. Duration 12 hours. Concurrent medication/care: spinal anesthesia was administered with bupivacaine (marcaine) and fentanyl in the operating room, and cesarean delivery was performed in a standard fashion without injecting local anesthetic into the incision. No long acting intrathecal narcotics were administered. All patients had pfannenstiel incisions.. Indirectness: No indirectness (n=46) Intervention 2: Oral Opioid - Immediate release. 2 tablets of oxycodone-acetaminophen immediately after completion of cesarean delivery. for 12 hours after the procedure, 2 tablets of oxycodone-acetaminophen were administered at fixed intervals every 3 hours. after 12 hours, 1 to 2 tablets were permitted every 4 hours as needed for pain, for a maximum of 12 tablets in 24 hours. after 24 hour study period, patients continued to receive ora oxycodone-acetaminophen and ibuprofen. all were discharged with these oral agents.. Duration 24+ hours. Concurrent medication/care: spinal anesthesia was administered with bupivacaine (marcaine) and fentanyl in the operating room, and cesarean delivery was performed in a standard fashion without injecting local anesthetic into the incision. No long acting intrathecal narcotics were administered. All patients had pfannenstiel incisions.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PATIENT CONTROLLED ANALGESIA versus IMMEDIATE RELEASE

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS 6 hours after the procedure at 6 hours; Group 1: mean 4.1 (SD 2.5); n=47, Group 2: mean 3.2 (SD 1.8); n=46
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VAS 24 hours after the procedure at 24 hours; Group 1: mean 4.1 (SD 2.1); n=47, Group 2: mean 2.9 (SD 1.7); n=46
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: additional medication at 24 hours; number of people receiving additional medication, IV group -3; Oral group - 4;
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Davis 2006[222]
Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: nausea 6h at 6 hours; Group 1: mean 2 (SD 3.4); n=47, Group 2: mean 0.2 (SD 0.9); n=46 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: nausea 24h at 24 hours; Group 1: mean 0.3 (SD 0.8); n=47, Group 2: mean 1 (SD 2); n=46 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Hospital readmission - Actual outcome: hospital readmission at not specified; Group 1: 0/47, Group 2: 0/46 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay

Study	Rothwell 2011[1071]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in United Kingdom; Setting: not stated
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients undergoing THR, age 60–85 yr, ASA health status class I–III, and willing to undergo spinal anaesthesia.
Exclusion criteria	Weight ,45 kg, long-term strong opioid therapy before operation (regular codeine or tramadol was permitted); abnormal

Study	Rothwell 2011[1071]
	preoperative mental status; inability to operate the IVPCA device; or known allergy to OOXY or morphine.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): OOXY 72 (60-79); IVPCA 71 (60-79). Gender (M:F): Define. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA status 1-3). 3. Type of surgery: ortho/large joint replacement (total hip replacement).
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: PCA - IV patient controlled analgesia. IV morphine boluses from the pump. IVPCA patients continued with the PCA until either they wished to discontinue it or they were using ,1mgh21. the pump in the IVPCA group. . Duration IVPCA patients continued with the PCA until either they wished to discontinue it or they were using ,1mgh21.. Concurrent medication/care: No premedication was given. Spinal anaesthesia was performed at an appropriate lumbar interspace in an aseptic fashion using standard 25 G Whitacre needles (Smiths Medical, Ashford, UK). Clonidine 75 mg in 0.5% hyperbaric bupivacaine was injected with a total injectate volume of 2.2–2.7 ml. Sedation was achieved with either i.v. midazolam or a continuous propofol infusion. Patients were given 1 mg of granisetron as antiemetic.. Indirectness: No indirectness (n=57) Intervention 2: Oral Opioid - Modified release. The OOXY group were given oral OOXY slow release (Oxycontin) 20 mg and were reminded to ask for additional oral analgesia when required. OOXY patients were given 20 mg controlled-release OOXY (OxycontinTM) 12 hourly for 3 days or until they wished to discontinue.. Duration 3 days. Concurrent medication/care: No premedication was given. Spinal anaesthesia was performed at an appropriate lumbar interspace in an aseptic fashion using standard 25 G Whitacre needles (Smiths Medical, Ashford, UK). Clonidine 75 mg in 0.5% hyperbaric bupivacaine was injected with a total injectate volume of 2.2–2.7 ml. Sedation was achieved with either i.v. midazolam or a continuous propofol infusion. Patients were given 1 mg of granisetron as antiemetic.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PATIENT CONTROLLED ANALGESIA versus MODIFIED RELEASE	

Study	Rothwell 2011[1071]
Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: pain at rest (mean score) 0-24 h at 24 h; Group 1: mean 1.73 (SD 2.32); n=55, Group 2: mean 1.65 (SD 2.21); n=55 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: nausea score at 24 hafter randomisation; Group 1: mean 0.7 (SD 1.41); n=55, Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to intolerable nausea and vomiting nausea or vomiting. ; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Dieterich 2012[243]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=239)
Countries and setting	Conducted in Germany; Setting: department of obstetrics and gynecology of the university of Rostock Germany
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	main inclusion criteria were CS in spinal anaethesia, no history of opioid or metamizol treatment, written consent and ability to use a PCA device.
Exclusion criteria	Exclusion criteria were CS in intubation anesthesia, use of peridural catheter for pre, peri or post-CS

Study	Dieterich 2012[243]
	analgesia, additional post-CS metamizol use, allergy/ or ibuprofen, chronic use of opioids or history of chronic pain syndrome.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): oral 28.5(5.9), PCA 29.8 (5.1). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Type of surgery:
Indirectness of population	No indirectness
Interventions	(n=126) Intervention 1: PCA - IV patient controlled analgesia. Patients assigned to PCA group received a single use, IV PCA device (2mg piriritramide/ml 0.9% saline, Vygon, Medical products, Aachen, Germany). A patient initiated IV bolus injection contained 1 mg piritramide with a lock out interval of 5 min. The maximum dose was limited to 30 mg piritramide equivalent to 40 mg oxycodone total dose. the PCA was discontinued after 24 hours.. Duration 24 hours. Concurrent medication/care: no additional local anesthetic was used. Regardless of randomisation, patients received oral ibuprofen 500 mg every 8 hours for baseline analgesia during the first day after cesarean. From the first day after cesarean, 500 mg ibuprofen and 1 g iacetaminophen were only offered as rescue medication on demand. Indirectness: No indirectness (n=113) Intervention 2: Oral Opioid - Immediate release. Patients received 20 mg Oxycodone at fixed intervals at 2 and 12 hours after the CS. Duration 12 hours. Concurrent medication/care: no additional local anesthetic was used. Regardless of randomisation, patients received oral ibuprofen 500 mg every 8 hours for baseline analgesia during the first day after cesarean. From the first day after cesarean, 500 mg ibuprofen and 1 g iacetaminophen were only offered as rescue medication on demand. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PATIENT CONTROLLED ANALGESIA versus IMMEDIATE RELEASE

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain (VAS) at 24 hours at 24 hours; Group 1: mean 4.85 (SD 2.23); n=126, Group 2: mean 5.88 (SD 2.01); n=113
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: general satisfaction with pain management at post intervention; Group 1: mean 8.4 (SD 2.1); n=126,
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting)

Study	Dieterich 2012[243]
- Actual outcome: rescue medication used at 24 hours; Mean; , Comments: reported as patients in need for rescue medication as a percentage in the graph; Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: Length of hospital stay at 24 hours; Length of hospital stay was reported as overall mean for all patients 4.2 days; Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	Striebel 1998[1202]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Germany; Setting: department of anaesthesiology
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	at least 1 day before surgery, ASA physical status I or II patients undergoing orthopedic surgery (17 and 19 internal fixations, and 10 and 7 other procedures (endoprosthesis, arthrodesis, external fixation for PCOA and PCIA
Exclusion criteria	addiction to opioids other drugs or alcohol or an allergy to opioids
Recruitment/selection of patients	not stated

Study	Striebel 1998[1202]
Age, gender and ethnicity	Age - Mean (SD): PCA 43.7 (15.9); Patient controlled oral analgesia PCOA 39.9 (13.1. Gender (M:F): 38/22. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: ortho/large joint replacement (orthopedic surgery (internal fixations, external fixation, endoprosthesis, arthrodesis)).
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: PCA - IV patient controlled analgesia. PCIA group (bolus 2.0 mg of morphine, lockout time 12 min, loading dose 2 mg, maximal dose 10 mg/h; n = 32). . Duration 1 day. Concurrent medication/care: Anesthesia was standardized in all patients. After the IV administration of 1 mg of vecuronium, 3-5 mg/kg thiopental, 0.1-0.2 mg of fentanyl, and an additional 0.08-0.1 mg/kg vecuronium were given. Tracheal intubation was established, and ventilation was controlled using a mixture of O,/N,O (1:2) adding enflurane to maintain arterial blood pressure and heart rate within an individually acceptable and stable range. (n=32) Intervention 2: Oral Opioid - Immediate release. PCOA group (maximal dose 20 mg of morphine per 60 min, loading dose 40 mg; n = 32) A 4% aqueous morphine solution (40 mg/mL) was used for PCOA. . Duration 1 day. Concurrent medication/care: Anesthesia was standardized in all patients. After the IV administration of 1 mg of vecuronium, 3-5 mg/kg thiopental, 0.1-0.2 mg of fentanyl, and an additional 0.08-0.1 mg/kg vecuronium were given. Tracheal intubation was established, and ventilation was controlled using a mixture of O,/N,O (1:2) adding enflurane to maintain arterial blood pressure and heart rate within an individually acceptable and stable range. . Indirectness: No indirectness Comments: PCOA - patient controlled ora anesthesia

Study	Striebel 1998[1202]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PATIENT CONTROLLED ANALGESIA versus IMMEDIATE RELEASE Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain intensity 100mm scale at 0 480 minutes; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: adverse events tiredness dizziness nausea at day 1; Group 1: 2/30, Group 2: 6/30 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Ong 2005[945]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in USA; Setting: not specified
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	72 patients undergoing elective surgical removal of impacted mandibular third molars in an outpatient setting participated in the study. All patients were ASA class 1 and older than 16 years and had at least 1 impacted mandibular third molar based on orthopantomogram evidence

Study	Ong 2005[945]
Exclusion criteria	history of hypersensitivity to tramadol or if they were taking sedatives. patients with recent history of pain due to infection at the proposed surgical site were excluded from the study. patients were not allowed to take any analgesics, such as NSAIDs for 1 week before the study.
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): iv 25.3 (3.9); oral 24.3 (4.3). Gender (M:F): IV 15/19; oral 16/18. Ethnicity: NA
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 3. Type of surgery: Not stated / Unclear (Third molar surgery).
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: PCA - IV patient controlled analgesia. 50-mg/mL injectable ampoules; injectable tramadol was diluted to 2 ml using physiologic saline. An intravenous cannula was inserted into the antecubital fossa or dorsum of the hand in all patients for the administration of drugs.. Duration 15 minutes preoperatively. Concurrent medication/care: n/a. Indirectness: No indirectness Comments: single bolus injection of Tramadol (n=36) Intervention 2: Oral Opioid - Immediate release. 50 mg capsules given 15 min preoperatively. Duration 15 minutes preoperatively. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV PATIENT CONTROLLED ANALGESIA versus IMMEDIATE RELEASE

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: pain VAS 100mm scale at 8 hours postsurgery; Group 1: mean 15.9 mm (SD 9.6); n=36, Group 2: mean 36.9 mm (SD 17.2); n=36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Pain (Global assessment score) 8 hours at 8 hours postsurgery; Group 1: mean 2.6 (SD 0.9); n=36, Group 2: mean 1.1 (SD 0.8); n=36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Acetaminophen consumption during first 8 hours at 8 hours postsurgery; Group 1: mean 1.823 (SD 1.266); n=36, Group 2: mean 3.558 (SD 1.418); n=36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Ong 2005[945]
- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Benzon 1993[98]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=36)
Countries and setting	Conducted in USA; Setting: Northwestern memorial hospital, Chicago , Illinois
Line of therapy	Not applicable
Duration of study	Intervention + follow up: surgery + 72 hours post-surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	36 patients who were scheduled to undergo thoracotomy and who presented with no contraindication or objection to epidural postoperative analgesia were enrolled after verbal and written informed consent.
Exclusion criteria	Patients who required postsurgical mechanical ventilation and those whose ability to communicate was suspect were excluded from the study
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): Epidural 56.4 (12.1); PCA 60.1 (10.7). Gender (M:F): overall 20/16; Epidural 10/8; PCA 10/8. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Continuous epidural - Fentanyl + Bupivacaine. Patients in the Epidural group received fentanyl in the epidural infusion and saline through the PCA machine. 45 minutes before the end of the surgery, patients in the epidural group were given fentanyl, 100 µg in 10 ml of saline, through their epidural catheter. Duration surgery +72 hours post-surgery. Concurrent medication/care: General anesthesia

Study	Benzon 1993[98]
	consisted of thiopental induction and maintenance with enflurane or isioflurane and nitrousoxide inoxygen. Fentanyl, 100-500 µg was given intravenously during the induction and maintenance periods of anesthesia. Indirectness: No indirectness (n=18) Intervention 2: PCA - Morphine. Patients in the PCA group were given morphine PCA device. Duration surgery +72 hours post-surgery. Concurrent medication/care: General anesthesia consisted of thiopental induction and maintenance with enflurane or isioflurane and nitrousoxide inoxygen. Fentanyl, 100-500 µg was given intravenously during the induction and maintenance periods of anesthesia. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FENTANYL + BUPIVACAINE versus MORPHINE Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: pain scores (TOTPAR scores day 1) at day 2 after the surgery; Group 1: mean 14.7 n/a (SD 1.5); n=16, Group 2: mean 12.8 n/a (SD 1.6); n=18 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 0 - Actual outcome: pain scores (TOTPAR scores day2) at day 2 after the surgery; Group 1: mean 16.2 n/a (SD 2.6); n=16, Group 2: mean 13.4 n/a (SD 1.7); n=18 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 0 - Actual outcome: pain scores (TOTPAR scores day3) at day 2 after the surgery; Group 1: mean 16.9 n/a (SD 2.6); n=16, Group 2: mean 14.7 n/a (SD 2.2); n=18 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: adverse events (pruritus, nausea and vomiting at day 2 after the surgery; Pruritus: Epidural group 72%; PCA group 28%; P<0.02 Mild nausea experienced by 30 - 50 % in both groups; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 0	
Protocol outcomes not reported by the	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount

Study	Benzon 1993[98]
study	of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Boylan 1998[125]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Canada; Setting: The Toronto Hospital
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II undergoing elective infrarenal aortic aneurysm repair or aortobifemoral bypass grafting
Exclusion criteria	coaulopathy or anticoagulant therapy precluding randomization to epidural; preoperative chronic analgesic use or substance dependance; previous adverse reactions (other than nausea) to narcotic analgesics; and documented cerebrovascular disease or other neuropsychiatric illness including a history of postoperative confusion
Recruitment/selection of patients	elective patients infrarenal aortic aneurysm repair or aorto-bifemoral bypass grafting
Age, gender and ethnicity	Age - Mean (SD): PCA: 68.1 ± 9.2; Epidural 69.9 ± 8.4. Gender (M:F): 33/7. Ethnicity: NA
Further population details	1. Age: >60 years (PCA: 68.1 ± 9.2; Epidural 69.9 ± 8.4). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (abdominal aortic surgery).
Indirectness of population	--
Interventions	(n=21) Intervention 1: PCA - Morphine. Postoperatively, PCA patients received nurse-administered morphine sulfate for analgesia until they were deemed able to use a PCA infusion device, programmed to deliver intravenous morphine sulfate 1mg bolus, with a 6 minute lock out period, a 4 hour maximum dose of 30mg and no continuous background infusion. . Duration Unclear. Concurrent medication/care: No other analgesic agents were used. . Indirectness: No indirectness Comments: Morphine

Study	Boylan 1998[125]
	(n=19) Intervention 2: Continuous epidural - Morphine + Bupivacaine. Epidural Bupivacaine-Morphine infusions (0.125% Bupivacaine and 0.1mg/ml morphine) were continued at 4ml/hour and adjusted in response to patient status. Inadequate analgesia (VAS > 4) was treated by a 5ml bolus of epidural 0.25% Bupivacaine and 0.05mf/kg morphine followed by an increase in the infusion rate by an increment of 2ml/h. . Duration Unclear. Concurrent medication/care: No other analgesic agents were used. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea / Vertigo at Postoperatively; Group 1: 3/21, Group 2: 1/19 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: Pruritis at Postoperatively; Group 1: 0/21, Group 2: 2/19 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: Complications - Other at Postoperatively; Group 1: 5/21, Group 2: 8/19; Comments: opioid antagonist; regimen failure; confusional state; pulmonary oedema; myocardial infarction; pneumonia; GI hemorrhage Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Length of stay in intensive care unit - Actual outcome: ICU stay at Postoperatively; Median (IQR) days, Comments: PCA: 2 (2 - 2) Epidural: 2 (1 - 2)); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: Hospital stay at admission to discharge; Median (IQR) days, Comments: PCA: 14 (13 - 15) Epidural: 13 (10 - 17)); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress

Study	Boylan 1998[125]
	and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of hospital stay ; Hospital readmission

Study	Bialka 2018[106]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in Poland; Setting: Medical University of Silesia, Poland.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: surgery + 48 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	All patients were aged between 18 and 77 years, a body mass index between 19–30 kg/m2, and had American Society of Anesthesiology (ASA) physical status between 1 and 3.
Exclusion criteria	Exclusion criteria were lack of consent, significant coagulopathy, contraindication to TEA or drugs used in protocol, history of chronic pain, chest wall neoplastic invasion, visible thoracic spine deformities, previous spine surgery, mental state preventing from effective use of PCA device.
Recruitment/selection of patients	enrolled 104 patients scheduled for elective anterolateral open thoracotomy between September 2013 to June 2014.
Age, gender and ethnicity	Age - Mean (SD): Epidural 63(9), PCA morphine 62(11); PCA Oxycodone 63(7). Gender (M:F): Epidural 14/19, PCA Morphine 15/17, PCA oxycodone. Ethnicity: Polish
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA status 1-3). 3. Type of surgery: Not applicable (Thoracotomy).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Continuous epidural - Fentanyl + Bupivacaine. As soon as the patients arrived in the postoperative care unit (PACU), the analgesic treatment was started as indicated by the randomization before surgery and lasted for the first 48 hours after end of surgery. Patients were thereafter given 1 g paracetamol intravenously on a 6-hour interval and 100 mg ketoprofen on a 12-hour interval as a rescue medication, if necessary. In patients assigned to the TEA group, a continuous epidural infusion consisting of

Study	Bialka 2018[106]
	0.1% bupivacaine combined with 0.0006% fentanyl with a rate according to the modified Bromage formula (0.8 mL/hour +0.05 mL for every 5 cm of height above 150 cm for every spinal segment) was started. Duration Surgery+ 48 hours post surgery. Concurrent medication/care: All patients were premedicated with up to 15 mg midazolam orallyGeneral anesthesia was induced with a combination of propofol of approximately 2 mg/kg, cisatracurium at approximately 0.15 mg/kg, and fentanyl at approximately 2 µg/kg. Additional doses were given as clinically indicated. Indirectness: No indirectness (n=35) Intervention 2: PCA - Morphine. Patients assigned to the MOR group, received boluses of 1–2 mg of morphine until pain visual analogic score (VAS) was at a maximum of 3 in the PACU. Afterwards the demand dose was a 1–2 mg bolus with a 5 min lockout, but no hourly limit. During the night, the basal rate was increased to 2–4 mg per hour. Duration Surgery+ 48 hours post surgery. Concurrent medication/care: All patients were premedicated with up to 15 mg midazolam orallyGeneral anesthesia was induced with a combination of propofol of approximately 2 mg/kg, cisatracurium at approximately 0.15 mg/kg, and fentanyl at approximately 2 µg/kg. Additional doses were given as clinically indicated. Indirectness: No indirectness (n=35) Intervention 3: PCA - Oxycodone. Patients assigned to the OXY group, received boluses of 1 mg of oxycodone until pain VAS score was at a maximum of 3 in the PACU. Afterwards the demand dose was a 1–2 mg bolus with a 5 min lockout, but no hourly limit. During the night, the basal rate was increased to 2–4 mg per hour. Duration Surgery+ 48 hours post surgery. Concurrent medication/care: All patients were premedicated with up to 15 mg midazolam orallyGeneral anesthesia was induced with a combination of propofol of approximately 2 mg/kg, cisatracurium at approximately 0.15 mg/kg, and fentanyl at approximately 2 µg/kg. Additional doses were given as clinically indicated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FENTANYL + BUPIVACAINE versus MORPHINE

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain (VAS) postoperative hour 4 at postoperative hour 4; Group 1: mean 2 n/a (SD 2); n=33, Group 2: mean 3 n/a (SD 1); n=32;
Comments: pain reported at postoperative hours (0, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48.) for this particular outcome score measured at 4th hour after the surgery was reported.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 2; Group 2 Number missing: 3
- Actual outcome: Pain (VAS) postoperative hour 24 at postoperative hour 4; Group 1: mean 2 n/a (SD 2); n=33, Group 2: mean 3 n/a (SD 1); n=32;
Comments: pain reported at postoperative hours (0, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48.) for this particular outcome score measured at 24th hour after

Study	Bialka 2018[106]
the surgery was reported. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3 - Actual outcome: Pain (VAS) postoperative hour 48 at postoperative hour 48; Group 1: mean 1 n/a (SD 1); n=33, Group 2: mean 2 n/a (SD 1); n=32; Comments: pain reported at postoperative hours (0, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48.) for this particular outcome score measured at 48th hour after the surgery was reported. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FENTANYL + BUPIVACAINE versus OXYCODONE Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain (VAS) postoperative hour 4 at postoperative hour 4; Group 1: mean 2 n/a (SD 2); n=33, Group 2: mean 3 n/a (SD 2); n=34; Comments: pain reported at postoperative hours (0, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48.) for this particular outcome score measured at 4th hour after the surgery was reported. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 2; Group 2 Number missing: 1 - Actual outcome: Pain (VAS) postoperative hour 24 at postoperative hour 4; Group 1: mean 2 n/a (SD 2); n=33, Group 2: mean 3 n/a (SD 2); n=34; Comments: pain reported at postoperative hours (0, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48.) for this particular outcome score measured at 24th hour after the surgery was reported. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 - Actual outcome: Pain (VAS) postoperative hour 48 at postoperative hour 48; Group 1: mean 1 n/a (SD 1); n=33, Group 2: mean 2 n/a (SD 1); n=34; Comments: pain reported at postoperative hours (0, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48.) for this particular outcome score measured at 48th hour after the surgery was reported. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Azad 2000[62]

Study	Azad 2000[62]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Germany; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	In all patients thoracotomy was performed for lobectomy, resection of lung tissue or transthoracalmediastinotomy
Exclusion criteria	Patients who refused one of the analgesic regiments or those with a history of addiction, chronic use of analgesics, severe pulmonary disease, advanced renal failure, impairment of primary or secondary haemostasis, as well as those with neurological disorders were excluded
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Range: 31 - 75 years. Gender (M:F): Epidural 6/19; PCA 8/17. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (Thoracotomy).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Continuous epidural - Fentanyl + Bupivacaine. mixture of bupivacaine 0.125 %/ ropivacaine 0.2% respectively and fentanyl 4.5 µg ml-1 the flow rate varied between 4 and 10 ml h-1 depending on the location of the catheter and the clinical demand. Duration intraoperative. Concurrent medication/care: In all patients general anesthesia was induced with iv administration of fentanyl 3 µg kg-1, thiopental 4-5 mg kg-1 and atracurium 0.5 mg kg-1 Anaesthesia was maintained with desflurane a mixture of oxygen and nitrous oxide (inspiratory oxygen concentration of 50 % during double-lung ventilation and100% during single lung ventilation) and repetetive application of atracurium. the first 12 consecutive patients received bupivacaine while all subsequent patients received ropivacaine. Intraoperative analgesia was obtained by single epidural injection of Fentanyl 1.5 µg kg-1 prior to surgical incision and repetetive injections of 3-5 ml bupivacaine 0.5%/ ropivacaine 0.75 % respectively. Indirectness: No indirectness (n=25) Intervention 2: PCA - Oxycodone. After arrival in the recovery room, patients in the PCA group, who complained of pain, received intravenous loading doses of piritramid 0.05 kg-1. PCA was initiated as soon

Study	Azad 2000[62]
	as the reported sufficient analgesia at rest and seemed to be awake enough for the PCA. PCA devices were filled with piritramid 25mg ml-1 and programmed to give 1ml bolus (2.5 mg) with 15 min lockout interval and dose limit of 25 mg within 4 hours. Duration surgery+after the surgery. Concurrent medication/care: In all patients general anesthesia was induced with iv administration of fentanyl 3 µg kg-1, thiopental 4-5 mg kg-1 and atracurium 0.5 mg kg-1 Anaesthesia was maintained with desflurane a mixture of oxygen and nitrous oxide (inspiratory oxygen concentration of 50 % during double-lung ventilation and100% during single lung ventilation) and repetitive application of atracurium. patients in the PCA group received only repetetive intravenous application of fentanyl 2 µg kg-1. Indirectness: No indirectness Comments: opioid used in the PCA group was piritramid
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FENTANYL + BUPIVACAINE versus OXYCODONE

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain at rest at post surgery post op day5; Mean; (p: <0.05), Comments: Pain outcome was reported in the graph only from the graph pain was measured at these times: 2 h post op; 5 hours post op; POD1; POD2; POD3; POD5; end of treatment);
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: nausea and vomiting at day of surgery - Postoperative day 5; Mean; , Comments: Common side effects (nausea, vomiting and pruritus) were reported using scale 0-2
Grade 0 - Patient reports no nausea/vomiting pruritus
Grade 1 - patient reports slight to moderate nausea/ vomiting/pruritus
grade 2 - patient reports severe nausea/vomiting/pruritus
Nausea/vomiting Op-day
GRADE 0 - EA/PCA (86/82); GRADE 1 - EA/PCA (6/8); GRADE 2 - EA/PCA (8/10)
Day 1 post-op
GRADE 0 - EA/PCA (90/72); GRADE 1 - EA/PCA (8/16); GRADE 2 - EA/PCA (2/12)
Day2 post-op
GRADE 0 - EA/PCA (96/84); GRADE 1 - EA/PCA (4/16); GRADE 2 - EA/PCA (0/0)
Day 3 post op
GRADE 0 - EA/PCA (91/76); GRADE 1 - EA/PCA (9/19); GRADE 2 - EA/PCA (0/5)
Day 5 post-op
GRADE 0 - EA/PCA (88/72); GRADE 1 - EA/PCA (12/21); GRADE 2 - EA/PCA (0/7)

Study	Azad 2000[62]
; Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Length of hospital stay - Actual outcome: Length of hospital stay at post-surgery; Group 1: mean 9.5 days (SD 0.5); n=25, Group 2: mean 11.1 days (SD 0.7); n=25 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	Carli 2002[147]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in USA; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention + follow up: surgery + 6 weeks after the surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	The target population for this study was adult patients undergoing elective colorectal surgery for nonmetastatic conditions
Exclusion criteria	Patients with malnutrition (serum albumin 35 g/l), severe cardiopulmonary disease (American Society of Anesthesiologists physical status IV), sepsis (febrile on antibiotics), inflammatory bowel disease, chemotherapy or radiotherapy within the 6 months preceding surgery, and an inability to communicate or understand the aim of the project (questionnaire and consent form would need to be translated) were ex-cluded.

Study	Carli 2002[147]
Recruitment/selection of patients	the study population was drawn from two adult hospital sites within the McGill University Health Centre from April 1998 and April 2000. The study was approved by the institutional ethics committees of the sites, and all 64 eligible patients agreed to participate in the study.
Age, gender and ethnicity	Age - Mean (SD): Epidural 59 (12); PCA 62 (12). Gender (M:F): Epidural 14/18; PCA 19/13. Ethnicity: not specified
Further population details	1. Age: Not stated / Unclear 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 4 3. Type of surgery: lower and upper GI (Colonic surgery).
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Continuous epidural - Fentanyl + Bupivacaine. An epidural infusion of bupivacaine 0.1% with 2 g/ml fentanyl at a rate between 4 and 15 ml/h was started at the end of surgery and continued for up to 4 postoperative days. Duration Surgery + 4 days post surgery. Concurrent medication/care: In the epidural group, an epidural catheter was inserted before general anesthesia in the eighth or ninth thoracic interspace, and bupivacaine 0.5% was injected in divided doses to a maximum of 15–20 ml in the epidural space to produce a bilateral segmental sensory block to ice and pinprick between T4and S5 dermatomes. The neural blockade was maintained during surgery with additional 5 ml bupivacaine 0.5% administered hourly. A light general anesthesia included induction with thiopentone, 100 g fentanyl, and vecuro-nium, and maintenance with 0.4% end-tidal isoflurane, nitrous oxide, and oxygen. Indirectness: No indirectness (n=32) Intervention 2: PCA - Morphine. Postoperative pain relief was with PCA morphine started at the end of surgery and continued for 4 days after surgery. The rate of infusion of intravenous morphine was set up at 1–2 mg every 5 min with no background infusion and increased if the visual analog scale (VAS; 0–100 mm) at rest was greater than 50. PCA was discontinued on days 3–4 after surgery if VAS on moving was less than 30. Duration surgery + 3/4 days after the surgery. Concurrent medication/care: Patients in the PCA group received general anesthesia consisting of thiopentone, 250 g fentanyl, vecuronium, and 1–1.5% end-tidal isoflurane, nitrous oxide, and oxygen. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FENTANYL + BUPIVACAINE versus MORPHINE

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain postoperative day1 at post op day 1; Group 1: mean 12 n/a (SD 23); n=32, Group 2: mean 34 n/a (SD 31); n=32
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Study	Carli 2002[147]
- Actual outcome: Pain postoperative day2 at post op day2; Group 1: mean 11 n/a (SD 17); n=32, Group 2: mean 33 n/a (SD 27); n=32 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: Pain postoperative day3 at post op day 3; Group 1: mean 13 n/a (SD 19); n=32, Group 2: mean 22 n/a (SD 21); n=32 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Functional measures - Actual outcome: 6 minute walking test difference from baseline values at 3 weeks after the discharge; Group 1: mean -32 Difference from baseline values (distance in meters measured preoperatively) - distance in meters measured 3 weeks after discharge (SD 62.6); n=32, Group 2: mean -62.9 Difference from baseline values (distance in meters measured preoperatively) - distance in meters measured 3 weeks after discharge (SD 74.5); n=32; Comments: 6 minute walking test- distance in meters walked in 6 minutes Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: 6 minute walking test difference from baseline values at 6 weeks after the discharge; Group 1: mean -5 Difference from baseline values (distance in meters measured preoperatively) - distance in meters measured 6 weeks after discharge (SD 59); n=32, Group 2: mean -21.7 Difference from baseline values (distance in meters measured preoperatively) - distance in meters measured 6 weeks after discharge (SD 48.3); n=32; Comments: 6 minute walking test - Distance in meters walked in 6 min Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Length of hospital stay - Actual outcome: Length of hospital stay at after the surgery; Group 1: mean 7 days (SD 4); n=32, Group 2: mean 8 days (SD 5); n=32 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 4: Hospital readmission - Actual outcome: hospital readmission at 4 days after the surgery; Group 1: 3/32, Group 2: 1/32 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Length of stay in intensive care unit

Study	OSLO-COMET trial: Hausken 2019[386]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=143)
Countries and setting	Conducted in Norway; Setting: Oslo university hospital
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 5 days post-op
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients diagnosed with colorectal cancer and liver metastases that could be radically resected by a parenchyma sparing liver resection, defined as resection of <3 consecutive liver segments.
Exclusion criteria	patients who could not accept, or previously had experienced adverse reactions to either of the 2 postoperative analgesic regimes
Age, gender and ethnicity	Age - Mean (SD): IV-PCA group 65.6 (62.8-68.4), thoracic epidural group 67,1 (64.8-69.3) . Gender (M:F): 85/58. Ethnicity: unclear
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Type of surgery:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: PCA - Oxycodone. IV-PCA – patients received IV ketorolac 30mg 3 x daily on post op days 0-3 (max 9 doses). IV ketorolac was substituted with diclofenac 3 x daily as tolerated. The IV-PCA consisted of ketobemidone 1 mg per dose, 8 minute lockout, max 7 doses per hour. . Duration 5 days post operatively. Concurrent medication/care: Both groups received 1g acetaminophen 4 x daily, dexamethasone as a single dose before surgery and oxycodone CR from post operative days 1 to 2.. Indirectness: No indirectness (n=77) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. patients received thoracic epidural of Bupivacaine 1mg/ml, Fentanyl 2mcg/ml and Epinephrine 2 mcg/ml at a rate of 5-15ml/h with 2 boluses of 5ml allowed per hour.. Duration 5 days post operatively. Concurrent medication/care: Both groups received 1g acetaminophen 4 x daily, dexamethasone as a single dose before surgery and oxycodone CR from post operative days 1 to 2.. Indirectness: No indirectness

Study	OSLO-COMET trial: Hausken 2019[386]
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OXYCODONE versus FENTANYL + BUPIVACAINE

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: mean pain score for post op days 1-5 at days 1 to 5 post op;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: no data for 24 hours post op; Group 1 Number missing: 2, Reason: switched to TEA but included in PCA group; Group 2 Number missing: 3, Reason: switched to PCA but included in TEA group

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: use of opoids on day 0 to 2 at use of additional medication;
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: switched to TEA but included in PCA group; Group 2 Number missing: 3, Reason: switched to PCA but included in TEA group

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: nausea and vomiting at 30 days post op; Group 1: 13/66, Group 2: 17/77
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: switched to TEA but included in PCA group; Group 2 Number missing: 3, Reason: switched to PCA but included in TEA group

Protocol outcome 4: Length of hospital stay
- Actual outcome: ICU length of stay at length of stay;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: switched to TEA but included in PCA group; Group 2 Number missing: 3, Reason: switched to PCA but included in TEA group
- Actual outcome: length of hospital stay at length of stay;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: switched to TEA but included in PCA group; Group 2 Number missing: 3, Reason: switched to PCA but included in TEA group

Protocol outcome 5: Hospital readmission
- Actual outcome: hospital readmission within 30 days at readmission within 30 days; Group 1: 5/66, Group 2: 8/77
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	OSLO-COMET trial: Hausken 2019[386]
- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: switched to TEA but included in PCA group; Group 2 Number missing: 3, Reason: switched to PCA but included in TEA group	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit

Study	Hubner 2015[414]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=128)
Countries and setting	Conducted in Switzerland; Setting: University Hospital of Lausanne
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients undergoing laparoscopic colorectal surgery
Exclusion criteria	Not reported
Recruitment/selection of patients	Patients selected from patients undergoing elective laparoscopic colorectal surgery
Age, gender and ethnicity	Age - Mean (SD): PCA: 61.2±17.8; Epidural: 63.1±15.1. Gender (M:F): Define. Ethnicity: NA
Further population details	1. Age: >60 years (PCA: 61.2±17.8; Epidural: 63.1±15.1). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA I - 13; ASA II - 90; ASA III - 19). 3. Type of surgery: lower and upper GI (laparoscopic colorectal surgery).
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: PCA - Morphine. iv PCA with morphine 1 mg/ml, with bolus of 1 ml at every 5 minutes and a locked of 40 mg/4 hours was inserted. Duration Unclear . Concurrent medication/care: All patients received paracetamol 4x1g/day and metamizole 4x500mg/day as baseline analgesic treatment unless contraindicated. Indirectness: No indirectness Comments: Morphine

Study	Hubner 2015[414]
	(n=67) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. a solution of bupivacaine 0.1%, fentanyl 2 µg/ml and adrenaline 2 µg/ml was initiated in the epidural group at a rate of 6-10 ml/h (target: VAS<4) with bolus of 3 ml of the solution allowed every 40 minutes (Patient Controlled Epidural Analgesia). Duration Unclear. Concurrent medication/care: All patients received paracetamol 4x1g/day and metamizole 4x500mg/day as baseline analgesic treatment unless contraindicated. Indirectness: No indirectness Comments: Fentanyl + Bupivacaine
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Complications (Clavien Dindo Grade I-IV) at postoperative to discharge; Group 1: 19/57, Group 2: 33/65; Comments: Medical and surgical complications
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: withdrawal from study; Group 2 Number missing: 2, Reason: withdrawal from study
- Actual outcome: Mortality at postoperative to discharge; Group 1: 0/57, Group 2: 2/65
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: withdrawal from study; Group 2 Number missing: 2, Reason: withdrawal from study

Protocol outcome 2: Length of stay in intensive care unit
- Actual outcome: Length of stay at High dependency unit at postoperatively; Median (IQR) days, Comments: PCA: 1 (0-1)
Epidural 1 (1-2.5)
p value 0.213);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: withdrawal from study; Group 2 Number missing: 2, Reason: withdrawal from study

Protocol outcome 3: Length of hospital stay
- Actual outcome: Length of hospital stay at postoperatively to discharge; Median (IQR) days, Comments: PCA: 5 (4-8)
Epidural: 7 (4.5-12)
P value 0.434);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: withdrawal from study; Group 2 Number missing: 2, Reason:

Study	Hubner 2015[414]
withdrawal from study Protocol outcome 4: Hospital readmission - Actual outcome: Readmission at post-discharge; Group 1: 0/57, Group 2: 3/65; Comments: p value = 0.247 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: withdrawal from study; Group 2 Number missing: 2, Reason: withdrawal from study	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures

Study	Kjolhede 2019[532]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Sweden; Setting: University hospital, Linkoping, sweden
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Women 18 to 70 years, with WHO performance status <2, with an American Society of Anesthesiologists (ASA) score <3 and speaking Swedish fluently were included.
Exclusion criteria	Contraindications against regional analgesia, physical or psychiatric disability and surgery where pain could not be expected to be controlled by the regional analgesia.
Recruitment/selection of patients	From March 2014 to January 2016, all women who were admitted to the Department of Obstetrics and Gynaecology, University Hospital, Linköping, Sweden due to a proven or assumed gynaecological abdominal malignancy were eligible for the study.

Study	Kjolhede 2019[532]
Age, gender and ethnicity	Age - Median (range): . Gender (M:F): 0/80. Ethnicity: unclear
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. Type of surgery:
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Spinal opioid (one administration) - Morphine + bupivacaine. Intrathecal morphine (ITM) - The allocated intervention of regional analgesic was applied prior to commencing the general anaesthesia. The experimental treatment group (the ITM) had an intrathecal combination of a single-dose isobar bupivacaine 15 mg, morphine 0.2 mg and clonidine 75 µg, preferably through a 25G spinal needle. The women in the ITM group received oral paracetamol 1330 mg and diclofenac 50 mg, both three times daily started on the day of surgery. Oxycodone 10–20 mg twice daily was added on the first postoperative day. Duration single injection prior to surgery. Concurrent medication/care: All women received a standardised premedication with paracetamol 1995 mg. The allocated intervention of regional analgesic was applied prior to commencing the general anaesthesia.Rescue opioids were the same for both groups; intravenous morphine, 0.5–1 mg, intravenou or oxycodone 5 mg orally was given if needed. In case of obvious pain relieving failure with the ITM or EDA, intravenous patient-controlled analgesia with morphine was started. . Indirectness: No indirectness (n=40) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. The EDA group had the standard EDA regime used in the hospital. The EDA was performed by a low thoracic puncture. The epidural infusion was started after induction of the general anaesthesia but before surgery by a bolus dose of fentanyl 50–100 µg and a bolus from a mixture of bupivacaine 2.4 mg/mL, adrenalin 2.4 µg/mL and fentanyl 1.8 µg/mL. The same mixture was used as a continuous infusion, typically 4–8 mL/hour, throughout surgery. The possibility of additional patient-controlled bolus doses of bupivacain 1 mg/mL+adrenalin 2 µg/mL+fentanyl 2 µg/mL were started postoperatively at the postoperative care unit and continued until the morning of the third postoperative day. The patients also had oral paracetamol 1330 mg three times daily, starting on the day of surgery. Oral oxycodone 10–20 mg twice daily and diclofenac 50 mg three times daily were added in the morning of the third postoperative day before removal of the epidural catheter according to the guidelines.. Duration 3 days post operatively. Concurrent medication/care: All women received a standardised premedication with paracetamol 1995 mg. The allocated intervention of regional analgesic was applied prior to commencing the general anaesthesia.Rescue opioids were the same for both groups; intravenous morphine, 0.5–1 mg, intravenou or oxycodone 5 mg orally was given if needed. In case of obvious pain relieving failure with the ITM or EDA, intravenous patient-controlled analgesia with morphine was started.. Indirectness: Serious indirectness; Indirectness comment: Epidural + use of additional PCA decided by responsible physician.

Study	Kjolhede 2019[532]
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE + BUPIVACAINE versus FENTANYL + BUPIVACAINE

Protocol outcome 1: Quality of life
- Actual outcome: QOL EQ-5D at pre op and weekly until 6 weeks post op;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: lost to follow up; Group 2 Number missing: 1, Reason: lost to follow up
- Actual outcome: QOL SF-36 at pre op and weekly until 6 weeks post op;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: lost to follow up; Group 2 Number missing: 1, Reason: lost to follow up

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: overall assessment of pain 0 to 6 days post op at 0 to 6 days post operatively;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: amount of equivalent morphine consumption at 0 to 6 days post operatively;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: complications: clavien dindo grade I at 6 weeks; Group 1: 8/40, Group 2: 13/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: complications: clavien dindo grade II at 6 weeks; Group 1: 6/40, Group 2: 6/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: complications: clavien dindo grade III at 6 weeks; Group 1: 6/40, Group 2: 1/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: complications: clavien dindo grade IV at 6 weeks; Group 1: 1/40, Group 2: 1/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Kjolhede 2019[532]
- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Length of stay in intensive care unit - Actual outcome: length of ICU stay at length of stay in ICU; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: lost to follow up; Group 2 Number missing: 0, Reason: lost to follow up Protocol outcome 6: Length of hospital stay - Actual outcome: length of hospital stay at length of stay; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: lost to follow up; Group 2 Number missing: 0, Reason: lost to follow up	
Protocol outcomes not reported by the study	Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Hospital readmission

Study	Liu 1995[626]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=54)
Countries and setting	Conducted in USA; Setting: Virginia Medical Centre & Mayo Clinic Jacksonville
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 2 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled to undergo partial resection of the colon.
Exclusion criteria	Aged <35 years or >80 years, ASA IV or V, history of chronic pain.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Mean: 62.5 (SE: 1). Gender (M:F): 15/11. Ethnicity: NA Not reported
Further population details	1. Age: >60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA <IV). 3. Type of surgery: lower and upper GI
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: PCA - Morphine. Received 5mg morphine intravenously after induction of GA. PCA morphine was begun in the postanaesthesia care unit after an initial loading dose. Initial settings were dose of 1 mg with lockout interval of 10 minutes. Analgesia at rest was titrated to a verbal pain score <5/10 with adjustments to PCA setting. . Duration 3 days. Concurrent medication/care: Intramuscular ketorolac 60 mg at the end of operation, continued 30 mg thereafter every 6 hours. . Indirectness: No indirectness (n=12) Intervention 2: Continuous epidural - Morphine + Bupivacaine. 3 ml 0.75% bupivacaine containing epinephrine (15 ug) followed by additional 7 ml 0.75% bupivacaine and 2mg morphine. Continuous epidural infusion of plain bupivacaine 0.1% with morphine 0.03 mg/ml-1 at a rate of 10ml/h-1. Duration 3 days. Concurrent medication/care: Intramuscular ketorolac 60 mg at the end of operation, continued 30 mg thereafter every 6 hours. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE versus MORPHINE + BUPIVACAINE	

Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: VAS: Pain at rest at n/a; Results not reported; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness - Actual outcome: VAS: Pain on ambulation at POD 1; Mean; (p: 0.01), Comments: Pain scores with morning ambulation were significantly lower with continuous epidural morphine and bupivacaine.); Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness - Actual outcome: VAS: Pain on ambulation at POD 2; Mean; (p: <0.01), Comments: Pain scores with morning ambulation were significantly lower with continuous epidural morphine and bupivacaine.); Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea at n/a; Group 1: 8/12, Group 2: 14/12; Comments: Average daily occurrence Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Madej 1992[652]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in United Kingdom; Setting: gynaecological unit of York District Hospital
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients scheduled to undergo total abdominal hysterectomy.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 42 (26-52). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: <60 years (Mean age 42). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (abdominal hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: PCA - Morphine. Self-administered i.v. diamorphine at a maximum rate of 1 mg every 5 min using a Graseby Patient Controlled Analgesia System. Duration 24 hours. Concurrent medication/care: One hour before operation, patients received temazepam 30 mg orally. Anaesthesia was induced with propofol 2 mg kg-1, followed by vecuronium 0.1 mg kg-1 and IPPV with nitrous oxide and enflurane in oxygen. After induction of anaesthesia, a lumbar extradural block was produced with 0.5 % bupivacaine 15-20 ml. Indirectness: No indirectness (n=20) Intervention 2: Continuous epidural - Morphine + Bupivacaine. Received an extradural infusion of 0.15% bupivacaine with 0.01% diamorphine 4-6 ml/h-1. Duration 24 hours. Concurrent medication/care: One hour before operation, patients received temazepam 30 mg orally. Anaesthesia was induced with propofol 2 mg kg-1, followed by vecuronium 0.1 mg kg-1 and IPPV with nitrous oxide and enflurane in oxygen. After induction of anaesthesia, a lumbar extradural block was produced with 0.5 % bupivacaine 15-20 ml. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAMORPHINE versus MORPHINE + BUPIVACAINE

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: VAS at 4 hours; Mean; , Comments: Pain scores at 4 hours post-operation showed no significant difference with continuous epidural morphine and bupivacaine and PCA diamorphine.;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: VAS at 12-24 hours; Mean; , Comments: Pain scores at 12-24 hours post-operation were significantly lower with continuous epidural morphine and bupivacaine compared to PCA diamorphine.;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Emetic sequelae at 24 hours; Group 1: 9/10, Group 2: 7/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Motamed 1998[765]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in France; Setting: Hospital (elective surgery)
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 28 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II, aged 18–70 yr due to undergo major abdominal surgery for cancer (midline or bisubcostal incision).
Exclusion criteria	Obesity, pulmonary disease, heavy smoking (more than 20 pack-years) and contraindication to extradural analgesia.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 58 (10). Gender (M:F): 20/37. Ethnicity: Not reported
Further population details	1. Age: >60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: PCA - Morphine. Intravenous morphine (1 mg bolus, 5-min lock-out and maximum dose 20 mg 4h-1). Duration 48 hours. Concurrent medication/care: In the recovery room, i.v. morphine was titrated in boluses of 3 mg every 10 min to achieve adequate pain relief by a four-point verbal scale (no pain;

	moderate pain; severe pain; very severe pain). No supplementary analgesia was given. Indirectness: No indirectness (n=30) Intervention 2: Continuous epidural - Morphine + Bupivacaine. An extradural infusion of 0.125% bupivacaine with morphine 0.25 mg/ml-1 was given at the rate of 10 ml/h-1. Duration 48 hours. Concurrent medication/care: After completion of surgery, in the recovery room, a bolus dose of 0.125% bupivacaine with morphine 0.25 mg ml-1 injected into the catheter to achieve a bilateral and symmetrical T6 sensory block. No supplementary analgesic was given during the first 48 h; if this was needed, the patient was withdrawn from the study. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE versus MORPHINE + BUPIVACAINE Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: VAS at 4 hours; Mean; (p: <0.05), Comments: VAS scores were significantly lower at 2, 8, and 24 h postoperatively in the EXI group at rest and while coughing. Values presented in a graph as median and IQR.); Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Morphine usage at 24 hours; Group 1: mean 40.6 mg (SD 17.5); n=29, Group 2: mean 5.9 mg (SD 2.3); n=28 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: PCA is controllable by patient; Group 1 Number missing: 1; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Owen 1993[948]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=43)
Countries and setting	Conducted in Australia; Setting: hospital (not reported)
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged between 18 and 75 years, ASA physical status 1 or 2 who were scheduled to undergo elective surgery through an upper abdominal incision.
Exclusion criteria	Patients with acute or chronic lung pathology, or documented sleep apnoea. or in whom epidural catheter placement was contraindicated were not studied.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 54 (15). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery:
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: PCA - Fentanyl. Patient-controlled analgesia (PCA); fentanyl bolus dose 25 ug with a 15 min lockout interval from a PCA pump. Duration 48 hours. Concurrent medication/care: Postoperatively, patients were transferred to the recovery room where boluses of fentanyl 25 ug were administered epidurally until satisfactory pain relief was achieved. In the recovery room all patients received supplemental oxygen at 6 I.min-I via a Hudson ‘see-thru’ adult oxygen mask. Indirectness: No indirectness (n=15) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. Fentanyl 50 ug.h-’ (10 ug.ml-I) along with nurse-administered fentanyl boluses of 25 ug. Duration 48 hours. Concurrent medication/care: Postoperatively, patients were transferred to the recovery room where boluses of fentanyl 25 ug were administered epidurally until satisfactory pain relief was achieved. In the recovery room all patients received supplemental oxygen at 6 I.min-I via a Hudson ‘see-thru’ adult oxygen mask. Indirectness: No indirectness

Funding	Study funded by industry (Abbott Australasia Pty. Ltd.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FENTANYL versus FENTANYL + BUPIVACAINE Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: VAS at Day 1; Group 1: mean 21 (SD 6); n=12, Group 2: mean 18 (SD 7); n=15; VAS 0-100 Top=High is poor outcome; Comments: Values read from a graph Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: VAS at Day 2; Group 1: mean 10.6 (SD 3.6); n=12, Group 2: mean 9.2 (SD 4.4); n=15; VAS 0-100 Top=High is poor outcome; Comments: Values read from a graph. Variance is 95% CI Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Paulsen 2001[990]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=49)
Countries and setting	Conducted in USA; Setting: University of Kansas, school of medicine
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	men or women ages ≥18 who were scheduled to undergo an elective small bowel or colon resection with a primary anastomosis.
Exclusion criteria	age < 18; steroid use; unprepped bowel for colon surgery; systemic anticoagulation; systemic infection; presence of gastrostomy or jejunostomy tube; platelet count <100,000; inability to communicate; presence of spinal stenosis; and unwillingness of the patient to participate.
Recruitment/selection of patients	Patients scheduled to undergo an elective small bowel or colon resection with a primary anastomosis
Age, gender and ethnicity	Age - Mean (SD): PCA ± 65.1 ± 12.2; Epidural 61.3 ± 13.4. Gender (M:F): 20/24. Ethnicity: NA
Further population details	1. Age: >60 years (PCA ± 65.1 ± 12.2; Epidural 61.3 ± 13.4). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (bowel resection).
Indirectness of population	--
Interventions	(n=25) Intervention 1: PCA - Morphine. Morphine was used at a dose of mg IV every 10 minutes with a 2mg every 4 hour lockout period. Meperidine hydrochloride was used at a dose of 10mg IV every 10 minutes with a 240mg every 4 hour lockout if the patient was allergic or could not tolerate morphine. if pain was not adequately controlled, then basal rates were started at a dose of 1mg/hour for those receiving morphine and 10mg/hour for those receiving meperidine hydrochloride. . Duration unclear - range of 2 days to 4 days . Concurrent medication/care: na. Indirectness: No indirectness Comments: Morphine (n=24) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. Postoperatively, epidural catheters were infused with fentanyl 5µg/ml and Bupivacaine 1mg/ml at a 10ml/hr for patients taller than 68 inches and 8ml/hour for those less than 68 inches tall. Duration unclear - range 2 - 8 days . Concurrent medication/care: na. Indirectness: No indirectness Comments: Fentanyl + bupivacaine

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain POD1 at postoperative day 1; Median (IQR) pain score, Comments: PCA: 39 (27-47) Epidural: 18 (5-47)); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 1 - Actual outcome: Pain POD2 at postoperative day 2; Median (IQR) pain score, Comments: PCA: 42 (24-48) Epidural: 17 (2-33)); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 1 - Actual outcome: Pain POD3 at postoperative day 3; Mean; (Median (IQR)) pain score, Comments: PCA: 39 (21 - 51) Epidural: 9.5 (0 - 31)); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 1 - Actual outcome: Pain POD4 at postoperative day 4; Median (IQR) pain score , Comments: PCA: 50 (38-54) Epidural: 25.5 (6-49.5)); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 1 Protocol outcome 2: Length of hospital stay - Actual outcome: Discharge interval per study criteria at postoperatively; Group 1: mean 3.9 days (SD 1.7); n=21, Group 2: mean 5.4 days (SD 2.7); n=23 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Radovanovic 2017[1025]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Serbia; Setting: Oncology Institute
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA physical status I-III, signed informed consent to participate in the study, and elective open colorectal cancer surgery performed.
Exclusion criteria	contraindication to placement of an epidural catheter and use of non steroidal anti-inflammatory drugs (NSAIDs), history of allergy to local anesthetics, NSAIDs or opioids, alcohol or drug abuse, pregnancy, palliative surgery, patient refusal and inability to communicate or understand the purpose of the study.
Recruitment/selection of patients	adult patients undergoing elective open colorectal resection at Oncology Institute of Vojvodina in Sremska Kamenica
Age, gender and ethnicity	Age - Mean (SD): PCA: 64.18 ± 9.90; Epidural: 65.88 ± 10.00. Gender (M:F): 38/22. Ethnicity: NA
Further population details	1. Age: >60 years (PCA: 64.18 ± 9.90; Epidural: 65.88 ± 10.00). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA I - 6; ASA II - 29; ASA III - 25). 3. Type of surgery: lower and upper GI (Colorectal cancer resection).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Continuous epidural - Fentanyl + Bupivacaine. Epidural infusion of levobupivacaine 1 mg/mL with fentanyl 3 µg/mL and adrenaline 2 µg/mL at a rate between 5 and 10 mL/h was started at the end of surgery and continued for up to postoperative day (POD) 3. Duration 3 days postoperatively. Concurrent medication/care: Ketorolac iv was given to both groups as a supplementary analgesic. The first dose (30 mg) was administered on patient arrival at the ICU. Ketorolac 15 mg was subsequently administered three times per day for 72 h. After 72 h, patients received oral ibuprofen 400 mg four times per day until discharge or up to POD 6. . Indirectness: No indirectness Comments: Fentanyl + Levobupivacaine (n=30) Intervention 2: PCA - Morphine. rate of infusion of iv morphine was set up at a bolus dose of 1-2 mg, lockout interval of 8 min, max 3 doses/h, with no background infusion. If VAS at rest was greater than 5, the lockout interval was reduced to 6 minutes, max 4 doses/h. If inadequate analgesia persisted, the bolus dose was increased in 0.5mg increments every second hour. . Duration 3 days postoperatively. Concurrent

	medication/care: Ketorolac iv was given to both groups as a supplementary analgesic. The first dose (30 mg) was administered on patient arrival at the ICU. Ketorolac 15 mg was subsequently administered three times per day for 72 h. After 72 h, patients received oral ibuprofen 400mg four times per day until discharge or up to POD 6. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus TEA Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Postoperative complications at postoperative to discharge; Group 1: 9/30, Group 2: 2/30; Comments: includes ileus, perineal infection, pleural effusion, distended abdomen, postoperative delirium Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Length of hospital stay - Actual outcome: Length of stay at admission to discharge; Group 1: mean 9.23 days (SD 1.794); n=30, Group 2: mean 9.13 days (SD 2.501); n=30 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Rauck 1994[1041]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 2 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	ASA status I-III patients undergoing upper abdominal surgery.
Exclusion criteria	Patients with respiratory impairment, hypersensitivity to morphine.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 44 (18-79). Gender (M:F): 6/24. Ethnicity: NA
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: PCA - Morphine. As the peritoneum was closed, patients received a bolus of 0.07mg/kg of morphine sulphate. Subsequent epidural injections of 2-5mg were administered on demand. A minimum of 60 minute delay between doses was used, based on peak analgesia data of epidural morphine. . Duration 2 days. Concurrent medication/care: Immediately before surgery all patients had thoracic epidural catheters inserted. Neither additional local anaesthetic or opioids were given intraoperatively. . Indirectness: No indirectness (n=15) Intervention 2: Continuous epidural - Morphine + Bupivacaine. As the peritoneum was closed, patients received a bolus of 0.03mg/kg of morphine sulphate and were immediately started on 0.01% morphine sulphate at 005mg/h-1. Infusion was titrated to maintain adequate pain relief and minimise side effects. . Duration 2 days. Concurrent medication/care: Immediately before surgery all patients had thoracic epidural catheters inserted. Neither additional local anaesthetic or opioids were given intraoperatively. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA: MORPHINE versus EPI: MORPHINE

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: VAS at 2 hours; Group 1: mean 4.8 (SD 1.8); n=15, Group 2: mean 3.9 (SD 2.3); n=15; VAS 0-10 Top=High is poor outcome; Comments: Scores given as 0-100 for pain relief, converted to 0-10 for pain score.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: VAS at Day 1; Group 1: mean 3.7 (SD 2.1); n=15, Group 2: mean 0.03 (SD 0.5); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: VAS at Day 2; Group 1: mean 3.9 (SD 1.7); n=15, Group 2: mean 0.08 (SD 1.1); n=15 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea and vomiting at 2 days ; Group 1: 3/15, Group 2: 4/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Length of hospital stay - Actual outcome: Hospital stay at n/a; Group 1: mean 9 days (SD 4.8); n=15, Group 2: mean 8 days (SD 12.5); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Royse 2003[1076]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in Australia; Setting: The Royal Melbourne Hospital
Line of therapy	--Please Select--
Duration of study	Intervention time: 1998 and 2001
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not specified
Exclusion criteria	Not specified
Recruitment/selection of patients	Not specified

Age, gender and ethnicity	Age - Mean (SD): Epidural: 64.2 ± 9.3; PCA: 65.1 ± 10.8. Gender (M:F): 60/16. Ethnicity: NA
Further population details	1. Age: >60 years (Epidural: 64.2 ± 9.3; PCA: 65.1 ± 10.8). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (New York Heart Association classification). 3. Type of surgery: Not stated / Unclear (Coronary artery bypass graft).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: PCA - Morphine. demand patient controlled intravenous morphine (1 mg bolus with 5 minute lockout period), which was continued until 6:00 am on postoperative day 3. Duration postoperative to day 3. Concurrent medication/care: Anesthesia consisted of midazolam (3 to 5 mg), propofol (2 to 4 infusion (2g/mL), and a 2-stage target controlled alfentanil g/mL, reduced to 0.05 g/mL after cardiopulmonary bypass. Indirectness: No indirectness (n=40) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. ropivacaine 0.2% with fentanyl 2µg/mL was infused at a rate of 5 to 14 mL per hour, adjusted to attain a sensory blockade of T1 to T10, and was ceased at 6:00 am on postoperative day 3. Duration Postoperative to day 3. Concurrent medication/care: Eight mL of 0.5% ropivacaine with 20µg of fentanyl was administered prior to induction of anesthesia . Indirectness: No indirectness Comments: Fentanyl + Ropivacaine
Funding	Other (The study is supported by grants from the National Heart Foundation of Australia; Australian Society of Anaesthetists; and AstraZeneca Pty, Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain at POD 1; Group 1: mean 0.8 (SD 1.8); n=39, Group 2: mean 0.02 (SD 0.2); n=37; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: requested alternative treatment; Group 2 Number missing: 3, Reason: 1 patient withdrew, 2 failed intervention
- Actual outcome: Pain at POD 2; Group 1: mean 1.2 (SD 2.7); n=39, Group 2: mean 0.1 (SD 0.4); n=37; Visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: requested alternative treatment; Group 2 Number missing: 3, Reason: 1 patient withdrew, 2 failed intervention
- Actual outcome: Pain at POD 3; Group 1: mean 0.3 (SD 1.1); n=39, Group 2: mean 0.2 (SD 1); n=37; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High,

	Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: requested alternative treatment; Group 2 Number missing: 3, Reason: 1 patient withdrew, 2 failed intervention Protocol outcome 2: Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) - Actual outcome: Depression at postoperative to discharge; Group 1: 6/29, Group 2: 3/23; Comments: Minnesota Multiphasic Personality Inventory 2 questionnaire (t score > 65 indicates disorder) PCA: 61.2 ± 11.0; Epidural: 54.6 ± 9.6 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: did not complete forms; Group 2 Number missing: 11, Reason: did not complete forms - Actual outcome: Posttraumatic stress at postoperative to discharge; Group 1: 7/23, Group 2: 3/29; Comments: Minnesota Multiphasic Personality Inventory 2 questionnaire (t scores > 65 indicates disorder) PCA: 57.9 ± 11.1; Epidural: 50.4 ± 10.1 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 17, Reason: did not complete forms; Group 2 Number missing: 11, Reason: did not complete forms Protocol outcome 3: Length of stay in intensive care unit - Actual outcome: Intensive care length of stay at Postoperative to step down; Group 1: mean 48.1 Hours (SD 18.1); n=39, Group 2: mean 45.6 Hours (SD 9.3); n=37 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: requested alternative treatment; Group 2 Number missing: 3, Reason: 1 patient withdrew, 2 failed intervention Protocol outcome 4: Length of hospital stay - Actual outcome: length of hospital stay at preoperative day to discharge; Group 1: mean 7.2 Days (SD 1.7); n=39, Group 2: mean 6.9 Days (SD 1.7); n=37 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: requested alternative treatment; Group 2 Number missing: 3, Reason: 1 patient withdrew, 2 failed intervention
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Symptom scores ; Functional measures ; Hospital readmission

Study	Senturk 2002[1129]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=85)
Countries and setting	Conducted in Turkey; Setting: University Hospital, Turkey
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA status II–III patients undergoing thoracotomy
Exclusion criteria	Exclusion criteria during the preoperative period were general contraindications for epidural anesthesia; a history of chronic pain; psychiatric disease; documented cardiac or vascular disease; history of myocardial infarction; arrhythmias; preoperative respiratory function tests showing a forced vital capacity 60% predicted, forced expiratory volume 1 s □60%, or both; renal insufficiency (creatinine □15 mg/dL); or liver dysfunction (aspartate aminotransferase, alanine aminotransferase, or both □40 U/L). A decision of inoperability was the intraoperative exclusion criterion. During the postoperative period, patients who were reoperated, who reported pain related to recurrence, metastases, or infections, or who died were excluded.
Recruitment/selection of patients	Selected from patients undergoing thoracotomy
Age, gender and ethnicity	Age - Mean (SD): PCA: 50 ± 11; Epidural: 50.57 ± 10.2. Gender (M:F): 56/13. Ethnicity: NA
Further population details	1. Age: <60 years (PCA: 50 ± 11; Epidural: 50.57 ± 10.2). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (Thoracotomy).
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: PCA - Morphine. patients received IV-PCA with morphine with a 5-mg initial dose, no basal infusion, and a 2-mg bolus dose with a 15-min lock-out time. Duration 48 hours postoperatively . Concurrent medication/care: 5-10 µg/kg boluses of fentanyl were given intermittently until 1 h before the end of surgery. Indirectness: No indirectness Comments: Morphine (n=57) Intervention 2: Continuous epidural - Morphine + Bupivacaine. 10-mL bolus of a solution of bupivacaine 0.1% plus 0.1 mg/mL morphine in saline was administered, followed by a 7mL/h infusion of the same solution continuously. Duration 48 hours postoperatively. Concurrent medication/care: 5-10 µg/kg boluses of fentanyl were given intermittently until 1 h before the end of surgery. Indirectness: No

	indirectness Comments: Bupivacaine + Morphine
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain at 4 hours at postoperatively at 4 hours; Group 1: mean 4.45 (SD 2.131); n=23, Group 2: mean 3.053 (SD 2.253); n=46; Visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 5, Reason: postoperative exclusion criteria; Group 2 Number missing: 11, Reason: postoperative exclusion criteria - Actual outcome: Pain at 12 hours at postoperatively at 12 hours; Group 1: mean 2.65 (SD 1.178); n=23, Group 2: mean 0.974 (SD 0.986); n=46; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: --; Group 1 Number missing: 5, Reason: postoperative exclusion criteria; Group 2 Number missing: 11, Reason: postoperative exclusion criteria - Actual outcome: Pain at 24 hours at postoperatively at 24 hours; Group 1: mean 1.9 (SD 1); n=23, Group 2: mean 0.309 (SD 1.402); n=46 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 5, Reason: postoperative exclusion criteria; Group 2 Number missing: 11, Reason: postoperative exclusion criteria - Actual outcome: Pain at 48 hours at postoperatively at 48 hours; Group 1: mean 1 (SD 0.4); n=23, Group 2: mean 0.104 (SD 0.306); n=46; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: --; Group 1 Number missing: 5, Reason: postoperative exclusion criteria; Group 2 Number missing: 11, Reason: postoperative exclusion criteria	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Steinberg 2002[1196]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	(n=48)
Countries and setting	Conducted in USA; Setting: Tufts University School of Medicine (spread across five different institutions)
Line of therapy	1st line
Duration of study	Intervention time: July 1997 - August 1998
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA < IV; 18 - 80 years of age; weight 50 - 110kg.
Exclusion criteria	contraindication to placement of an epidural catheter and use of NSAIDS, history of allergy to local anesthetics or opioids, presence of bowel obstruction or inflammatory bowel disease, planned total colectomy or colostomy, previous history of abdominal radiation, recent use of corticosteroids, alcohol or drug abuse, pregnancy, and patient refusal.
Recruitment/selection of patients	selected from patients undergoing elective partial colon resection at 5 different institutions.
Age, gender and ethnicity	Age - Mean (SD): PCA: 61 ± 15; Epidural: 61 ± 10. Gender (M:F): 25/16. Ethnicity: NA
Further population details	1. Age: >60 years (PCA: 61 ± 15; Epidural: 61 ± 10). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA I - 5; ASA II- 29; ASA III - 7). 3. Type of surgery: lower and upper GI (open colon surgery).
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: PCA - Morphine. On arrival in the PACU, patients received boluses of IV morphine (2 to 3 mg every 3 - 5 minutes) as needed to achieve a verbal pain score below 50 (on a scale of 0 to 100) at rest. A PCA device was then connected. The device delivered 1mg IV bolus doses of morphine with an 8 minute lock out time. If analgesia was inadequate (verbal pain score >50/100), the lockout interval was reduced to 6 minuted. If inadequate analgesia persisted, the bolus dose was increased to 0.5mg increments every second hour. No background infusion was allowed. Treatment with PCA was continued until the predetermined discharge criteria of adequate pain control with oral medication was met or for a maximum of 6 days. . Duration predetermined discharge criteria of adequate pain control with oral medication OR maximum of 6 days. Concurrent medication/care: Ketorolac IM or IV was given to both groups as a supplementary analgesic. The first dose 15mg was administered on patient arrival at the PACU. Ketorolac 15mg was subsequently administered four times per day for 72 hours. After 72 hours, patients received oral ibuprofen 400mg four times a day until discharge or postoperative day 6. . Indirectness: No indirectness (n=20) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. Continuous epidural infusion of the solution of ropivacaine 2mg/ml plus fentanyl 2µg/ml was commenced at a rate of 8ml/hour within 1 hour after

	induction of general anesthesia and continued during the surgical procedure. On arrival to PACU, the rate of epidural infusion was reduced to 4ml/hr. In case of inadequate pain relief, defined as verbal pain score at rest of 50 or above (on a scale of 0 - 100), a bolus injection of 5ml of epidural solution (ropivacaine 2mg/ml plus fentanyl 2µg/ml) was administered after 15 minutes and if necessary a second bolus injection was given after 30 minutes. If analgesia was inadequate after 2 bolus injections, a test dose of 4 to 6 ml of ropivacaine 7.5mg/ml was administered and the sensory block level checked. In addition to receiving the continuous epidural infusion, the patient was able to obtain additional bolus injections by using a patient controlled epidural analgesia device set to deliver 2ml or ropivacaine / fentanyl infusion with a lock out of 15 minutes. If the patient had insufficient pain relief despite pressing the PCEA button more than once per hour, the basal infusion rate of ropivacaine/fentanyl infusion was increased in increments of 2mL/hr. . Duration postoperative to predetermined discharge criteria of adequate pain control with oral medication was met or a maximum of 6 days. Concurrent medication/care: Ketorolac IM or IV was given to both groups as a supplementary analgesic. The first dose 15mg was administered on patient arrival at the PACU. Ketorolac 15mg was subsequently administered four times per day for 72 hours. After 72 hours, patients received oral ibuprofen 400mg four times a day until discharge or postoperative day 6. . Indirectness: No indirectness Comments: ropivacaine + fentanyl
Funding	Equipment / drugs provided by industry (supported by a grant from Astra Zeneca LP)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL

Protocol outcome 1: Length of hospital stay
- Actual outcome: Hospital discharge at admission to discharge; Median (IQR) days, Comments: PCA: 4.8 (3.8 - 30.0)
Epidural: 5.0 (2.0 - 18.7));
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: --
- Actual outcome: Complication - Nausea at Postoperative to discharge; Group 1: 3/21, Group 2: 4/20
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: --
- Actual outcome: Complication - Vomiting at Postoperative to discharge; Group 1: 1/21, Group 2: 0/20
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: --
- Actual outcome: Complication - Hypotension at Postoperative to discharge; Group 1: 0/21, Group 2: 10/20
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: --
- Actual outcome: Complication - Pruritis at Postoperative to discharge; Group 1: 2/21, Group 2: 7/20
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: --	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Taqi 2007[1242]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Canada; Setting: McGill University Health Centre
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Scheduled to undergo elective laparoscopic colorectal surgery for benign and malignant colorectal lesions
Exclusion criteria	The exclusion criteria specified patients who had open colorectal resection, a history of chemoradiation within the 6 months preceding surgery, a contraindication to the epidural technique, and inability to communicate or understand the purpose of the study.
Recruitment/selection of patients	50 consecutive patients scheduled to undergo elective laparoscopic colorectal surgery for benign and malignant colorectal lesions were approached 2 weeks before surgery
Age, gender and ethnicity	Age - Mean (SD): PCA: 61.24 ± 14.91; Epidural: 65 ± 16.18. Gender (M:F): 27/23. Ethnicity: NA
Further population details	1. Age: >60 years (PCA: 61.24 ± 14.91; Epidural: 65 ± 16.18). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA I 5; ASA II 32; ASA III 13). 3. Type of surgery: lower and upper GI (laparoscopic colon resection).
Indirectness of population	--
Interventions	(n=25) Intervention 1: PCA - Morphine. Postoperative pain relief was with PCA using intravenous morphine started at the end of surgery and continued up to 3 days after surgery. The PCA was set up at 1 to 2 mg every 5 min with no background infusion, and was increased if the VAS at rest exceeded 5. Duration 72

	hours postoperatively. Concurrent medication/care: Both groups also received 500 mg naproxen twice a day either orally or rectally for 4 days, and acetaminophen 1 g four times a day for 4 days. Oral codeine up to 60 mg/day and acetaminophen 4 g/day were prescribed before discharge. Oxygen therapy (30% oxygen mask) was provided to all patients during the first 24 h. Indirectness: No indirectness Comments: Morphine (n=25) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. An epidural infusion of Bupivacaine 0.1% with 3 µg/ml fentanyl at a rate of 5 to 15 ml/h was started at the end of surgery and continued up to 3 postoperative days. Duration 72 hours postoperatively. Concurrent medication/care: Both groups also received 500 mg naproxen twice a day either orally or rectally for 4 days, and acetaminophen 1 g four times a day for 4 days. Oral codeine up to 60 mg/day and acetaminophen 4 g/day were prescribed before discharge. Oxygen therapy (30% oxygen mask) was provided to all patients during the first 24 h. Indirectness: No indirectness Comments: Fentanyl + Bupivacaine
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain POD 1 at POD 1; Median (IQR) pain score Visual Analogue scale 0-10 Top=, Comments: PCA: 4 (2.74 – 5.02)
Epidural: 1 (0.80 – 2.09);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain POD 2 at POD 2; Median (IQR) pain score visual analogue scale 0-10 Top=High is poor outcome, Comments: PCA: 3 (1.98 – 4.18)
Epidural: 0 (0.39 – 1.54)
;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain POD 3 at POD 3; Median (IQR) pain score visual analogue scale 0-10 Top=High is poor outcome, Comments: PCA:3 (1.67 – 3.69)
Epidural:3 (1.67 – 3.69)
;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain POD 4 at POD 4; Median (IQR) pain score visual analogue scale 0-10 Top=High is poor outcome, Comments: PCA:2 (1.17 – 3.23)
Epidural: 2 (1.17 – 3.23);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Nausea POD 1 at POD 1; Group 1: 16/25, Group 2: 10/25 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting POD 1-4 at POD 1-4; Group 1: 24/25, Group 2: 9/25 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Complications at Intraoperative + Postoperative; Group 1: 7/25, Group 2: 7/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: Length of hospital stay at Postoperatively - discharge; Median (IQR) days, Comments: PCA: 5 (4.23 - 9.53) Epidural: 5 (4.65 - 6.16)); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Hospital readmission - Actual outcome: Readmission at Postoperatively 30 days; Group 1: 2/25, Group 2: 2/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit

Study	**Tenenbein 2008[1251]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Canada; Setting: Departments of Anesthesia, Radiology, and Cardiology, Health Sciences Centre, University of Manitoba, Winnipeg, Manitoba, Canada
Line of therapy	1st line
Duration of study	Intervention time: July 2003 - June 2004

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients less than 80 yr of age, who were deemed appropriate for the facilitated recovery program
Exclusion criteria	previous cardiac surgery; combined procedures; serum creatinine greater than 150 mmol·L–1 ; pre-existing coagulopathy, or use of antiplatelet agents other than ASA; active liver disease; severe spinal deformity; ejection fraction less than 30%; and a body mass index > 35 kg·m–2
Recruitment/selection of patients	Patients scheduled for elective or semi-elective CABG surgery, between July 1, 2003 and June 30, 2004, were invited to participate
Age, gender and ethnicity	Age - Mean (SD): PCA: 60.8±9.4; Epidural: 60.1±6.3. Gender (M:F): not specified . Ethnicity: NA
Further population details	1. Age: >60 years (PCA: 60.8±9.4; Epidural: 60.1±6.3). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not stated / Unclear (Coronary artery bypass graft).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: PCA - Morphine. 1.0mg iv boluses with a five-minute lockout for 48 hr. Duration 48 hours postoperatively. Concurrent medication/care: Initial bolus of morphine 0.1 mg·kg–1, followed by PCA. Patients in both groups also received indomethacin suppositories (100 mg), postoperatively, and twice daily naproxen (500 mg), according to our usual practice, so long as no contraindications existed. (n=25) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. 0.2% ropivacaine, with 15 µg·mL–1 of hydromorphone. Duration 48 hours postoperatively. Concurrent medication/care: Patients in both groups also received indomethacin suppositories (100 mg), postoperatively, and twice daily naproxen (500 mg), according to our usual practice, so long as no contraindications existed. Indirectness: No indirectness Comments: Ropivacaine + Hydromorphone
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain 4 hours postoperatively at 4 hours postoperatively; Group 1: mean 3.6 score (SD 2.3); n=23, Group 2: mean 1.1 score (SD 1.2); n=23; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: unclear; Group 2 Number missing: 2, Reason: unclear Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: Pain POD 1 at 24 hours postoperatively; Group 1: mean 2.55 score (SD 1.619); n=23, Group 2: mean 0.85 score (SD 1.305); n=23; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: unclear; Group 2 Number missing: 2, Reason: unclear - Actual outcome: Pain POD 2 at 48 hours postoperatively; Group 1: mean 1.25 score (SD 1.226); n=23, Group 2: mean 0.4 score (SD 0.771); n=23; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: unclear; Group 2 Number missing: 2, Reason: unclear - Actual outcome: Pain POD 3 at 72 hours postoperatively; Group 1: mean 0.85 score (SD 1.101); n=23, Group 2: mean 0.7 score (SD 1.451); n=23; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: unclear; Group 2 Number missing: 2, Reason: unclear	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**George 1994[324]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=21)
Countries and setting	Conducted in United Kingdom; Setting: Belfast city hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	21 adult patients, ASA status I or II in the age range 20-74 years and undergoing upper abdominal surgey were included.

Exclusion criteria	Not specified
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): Epidural 43(14), PCA 44 (21). Gender (M:F): Define. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and ASA 2). 3. Type of surgery: lower and upper GI (upper abdominal surgery).
Indirectness of population	No indirectness: n/a
Interventions	(n=10) Intervention 1: Continuous epidural - Fentanyl + Bupivacaine. the patients for epidural analgesia received a 5 ml epidural bolus of a mixture of fentanyl 10 µg/ml with Bupivacaine 02 %,. this was followed by an Epidural infusion of the same solution initially at 5 ml/hr. Duration surgery plus follow-up. Concurrent medication/care: All patients were premedicated with temazepam 10 mg 1.5 hours before the operation. Fentanyl 100 µg and Bupivacaine 40 mg in a total volume of 10 ml was injected and after 15 min the upper an lower sensory were determined using a cold stimulus (ethyl chloride spray). maintenance of anesthesia was with isoflurane in nitrous oxide and oxygen with controlled ventilation. All patients received continuous 40% humidified oxygen at 5 ml/min. Aquapack and physiotherapy once on the evening of the operation, and three times the day after. Indirectness: No indirectness (n=11) Intervention 2: PCA - Morphine. Morphine was given by one of the investigators at 1mg per min intravenously to maximum of 20 mg or until patient was comfortable. The PCA device was the activated. background infusion was provided at 1 mg/hr and the patients request for analgesia was answered with 2 mg intravenous. There was a lockout period of 15 min after each successfull request and there was no 4 h limit set. Duration Surgery+ follow-up. Concurrent medication/care: All patients were premedicated with temazepam 10 mg 1.5 hours before the operation. Fentanyl 100 µg and Bupivacaine 40 mg in a total volume of 10 ml was injected and after 15 min the upper and lower sensory were determined using a cold stimulus (ethyl chloride spray). maintenance of anesthesia was with isoflurane in nitrous oxide and oxygen with controlled ventilation. All patients received continuous 40% humidified oxygen at 5 ml/min. Aquapack and physiotherapy once on the evening of the operation, and three times the day after. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FENTANYL + BUPIVACAINE versus MORPHINE

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score <6 hours at < 6 hours after the surgery; Pain was reported as a graph median (range)
2 hours after the operation
Epidural ~ 0 (0-5); PCA ~ 60 (15 -98)

6 hours after the operation Epidural ~ 0 (0-25); PCA ~ 42 (2 - 65); Risk of bias: All domain - High, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: pain score >6-24 hours at 6 - 24 hours after the surgery; Mean; , Comments: Pain was reported as a graph median (range) 12 hours after the operation Epidural ~ 1 (0-26); PCA ~ 8 (2 -58) 18 hours after the operation Epidural ~ 2 (0-22); PCA ~ 21 (0 - 90) 24 hours after the operation Epidural ~ 1 (0-20); PCA ~ 18(0 - 70); Risk of bias: All domain - High, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Emetic symptoms at 24 hors post-surgery; Mean; , Comments: Reported as incidence Epidural group - 0; PCA - 5; Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Tsui 1997[1268]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=122)
Countries and setting	Conducted in Hong Kong (China); Setting: Queen Mary Hospital, Hong Kong
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II female patients scheduled for gynecological lower abdominal operations through a vertical midline incision
Exclusion criteria	>65 years of age; mental defect; contraindications to regional block; significant cardiopulmonary dysfunction or abdominal incision other than vertical midline.
Recruitment/selection of patients	Patient scheduled for gynecological lower abdominal operations
Age, gender and ethnicity	Age - Mean (SD): PCA: 48 ± 11; Epidural: 51 ± 16. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (PCA: 48 ± 11; Epidural: 51 ± 16). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (All patients ASA I or II). 3. Type of surgery: Not stated / Unclear (Gynecological laparotomy).
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: PCA - Morphine. Patients received incremental IV boluses of morphine 1mg every 5 minutes in the recovery room, to achieve a VRS at rest of 3 or less. PCA morphine was then commenced using a Graseby Model 3300 PCA pump: morphine concentration 1mg/ml: PCA bolus 1mg; lockout interval 5 minutes and one hour maximum dose 0.1mg/kg. No basal infusion was given. . Duration 48 hours postoperatively. Concurrent medication/care: NA. Indirectness: No indirectness (n=57) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. Epidural infusion of bupivacaine 0.0625% and fentanyl 3.3µg/ml in normal saline at 10ml/h using a Graseby 3100 syring pump, commencing intraoperatively 30 minutes after the first bolus dose of bupivacaine. . Duration 48 hours postoperatively. Concurrent medication/care: If analgesia was inadequate in the recovery room (VRS at rest of 3 or higher), further epidural blousus of plain bupivacaine 0.25% of 5ml each were given every 15 minutes until adequate pain relief was received. . Indirectness: No indirectness Comments: fentanyl + bupivacaine

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Complications - Nausea at postoperative to discharge; Group 1: 29/54, Group 2: 30/57
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness
- Actual outcome: Complications - Vomiting at postoperative to discharge; Group 1: 20/54, Group 2: 19/57
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness
- Actual outcome: Complications - Pruritis at postoperative to discharge; Group 1: 5/54, Group 2: 18/57
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness
- Actual outcome: Complications - Hypotension at postoperative to discharge; Group 1: 0/54, Group 2: 0/57
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness
- Actual outcome: Complications - Respiratory depression at postoperative to discharge; Group 1: 0/54, Group 2: 0/57
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness
- Actual outcome: Complications - Dizziness at postoperative to discharge; Group 1: 20/54, Group 2: 11/57
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Wheatley 1990[1350]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in United Kingdom; Setting: District general hospital / university hospital
Line of therapy	1st line

Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	scheduled for general anesthesia and lower abdominal surgery
Exclusion criteria	not specified
Recruitment/selection of patients	patients selected from those scheduled for general anesthesia and lower abdominal surgery
Age, gender and ethnicity	Age - Mean (range): PCA: 40.2 (28-51); Extradural 43.2 (35-52). Gender (M:F): not specified. Ethnicity: NA
Further population details	1. Age: <60 years (PCA: 40.2 (28-51); Extradural 43.2 (35-52)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (All patients ASA I or II). 3. Type of surgery: lower and upper GI (lower abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: PCA - Morphine. patients self-administered i.v. diamorphine at a maximum rate of 1 mg every 20 min, commenced within 1 hour of surgery. Duration 24 hours postoperatively. Concurrent medication/care: na. Indirectness: No indirectness Comments: Diamorphine (n=10) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. extradural diamorphine in doses of 3.6 mg in saline 9 ml administered by the anesthetist or senior nursing staff as requested by the patient. This was repeated as necessary during the 24 hour period. . Duration 24 hours postoperatively . Concurrent medication/care: na. Indirectness: No indirectness Comments: extradural diamorphine
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EXTRADURAL

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain at 4 hours postoperatively at 4 hours postoperatively; Group 1: mean 31 (SD 9); n=10, Group 2: mean 6 (SD 5); n=10; visual analogue scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: pain at 6 - 24 hours postoperatively at 6 - 24 hours postoperatively; Group 1: mean 17.8 (SD 5.418); n=10, Group 2: mean 18.2 (SD

12.48); n=10; visual analogue scale 0-100 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Postoperative complications at postoperative ; Group 1: 3/10, Group 2: 8/10; Comments: need for catheter Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Complications - Vomiting at postoperative ; Group 1: 0/10, Group 2: 3/10 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Complications - Itching at postoperative ; Group 1: 1/10, Group 2: 3/10 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Wongyingsinn 2012[1363]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Canada
Line of therapy	1st line
Duration of study	Intervention time: October 2010 and April 2011
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients undergoing elective laparoscopic colon resection and >18 yr were enrolled in the study
Exclusion criteria	rectal resection, ASA.III, contraindication to spinal analgesia including infection at the site of injection and coagulopathy, chronic use of opioid, liver or renal impairment, and inability to communicate in either French or English.

Recruitment/selection of patients	Selected from patients undergoing elective laparoscopic colon resection
Age, gender and ethnicity	Age - Median (IQR): Spinal: 65 (39-85); PCA: 65 (34-83). Gender (M:F): 22/27. Ethnicity: NA
Further population details	1. Age: >60 years (Spinal: 65 (39-85); PCA: 65 (34-83)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA I - 11; ASA II - 32; ASA III - 6). 3. Type of surgery: lower and upper GI (laparoscopic colonic resection).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Spinal opioid (one administration) - Morphine + bupivacaine. isobaric bupivacaine 0.5% (10mg) together with preservative-free morphine was injected. The dose of morphine was based on patient's age, with 200µg in patients aged ≤75 yr and 150µg in patients aged >75 yr. Duration 48 hours postoperatively. Concurrent medication/care: For postoperative analgesia, oral oxycodone 5–10 mg was prescribed every 3 h for the first 48 h as a breakthrough medication, if NRS pain at rest was more than 3. All patients received oral acetaminophen and naproxen daily for up to five postoperative days. Indirectness: No indirectness (n=25) Intervention 2: PCA - Morphine. patients received i.v. morphine delivered via a PCA pump to deliver 1 mg every 7 min with no background infusion, which was set up in the post-anaesthesia care unit (PACU). Duration 48 hours postoperatively . Concurrent medication/care: PCA was discontinued 48h after surgery, and oral oxycodone 5–10 mg was then provided every 3 h as a breakthrough medication. All patients received oral acetaminophen and naproxen daily for up to five postoperative days. Indirectness: No indirectness
Funding	Other (Department of Anaesthesia, MUHC, Montreal, Quebec, Canada.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SPINAL versus PCA

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: pain at 24 hours at 24 hours postoperatively; Median (IQR) Visual analogue scale 0-10 Top=High is poor outcome, Comments: Spinal: 0 (0-1.5)
PCA: 2 (1-4)
p value 0.004;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0
- Actual outcome: pain at 48 hours at 48 hours postoperatively; Mean; (median (IQR)) visual analogue scale 0-10 Top=High is poor outcome, Comments: Spinal: 0 (0-2)
PCA: 1 (0-4)

p value 0.15;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0
- Actual outcome: pain at 72 hours at 72 hours postoperatively; median (IQR) visual analogue scale 0-10 Top=High is poor outcome, Comments: Spinal: 0 (0-3)
PCA: 0 (0-2.5)
p value 0.87;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Complications - Other at postoperatively; Group 1: 7/24, Group 2: 4/25; Comments: Oversedation, Ileus, Anaemia requiring blood transfusion, Tachycardia, Anastomotic abscess, Fever, Respiratory distress
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0
- Actual outcome: Complications - Respiratory depression at postoperatively; Group 1: 1/24, Group 2: 0/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0
- Actual outcome: Complications - Nausea at postoperatively; Group 1: 5/24, Group 2: 6/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0
- Actual outcome: Complications - Vomiting at postoperatively; Group 1: 5/24, Group 2: 5/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0
- Actual outcome: Complications - Pruritis at postoperatively; Group 1: 2/24, Group 2: 0/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0

Protocol outcome 3: Length of hospital stay
- Actual outcome: Length of stay at admission to discharge; Median (IQR) days, Comments: Spinal: 3 (3-4)
PCA: 3 (3-4)
p value 0.59);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0

Protocol outcome 4: Hospital readmission
- Actual outcome: Readmission at within 30 days postoperatively; Group 1: 1/24, Group 2: 1/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: converted procedure ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit

Study	**Zejun 2018[1428]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=99)
Countries and setting	Conducted in China; Setting: Affiliated Hospital of Qingdao University, China
Line of therapy	1st line
Duration of study	Intervention + follow up: January and 9 May 2017
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients qualified for VATS lobectomy as a result of cancer; aged 18–70 years; of either gender; and ASA status I–III
Exclusion criteria	technical failure to insert an epidural catheter; conversion of VATS to thoracotomy; discontinuation of local anesthesia for technical reasons (e.g. catheter slipping out or damage); aged < 18 years; unable to provide informed consent; and medical contraindication for TEA according to institutional guidelines
Recruitment/selection of patients	All patients undergoing elective VATS lobectomy at the Affiliated Hospital of Qingdao University, China were assessed for eligibility
Age, gender and ethnicity	Age - Mean (SD): PCA: 54.9 ± 11.7; Epidural: 57.8 ± 8.1. Gender (M:F): 56/42. Ethnicity: NA
Further population details	1. Age: <60 years (PCA: 54.9 ± 11.7; Epidural: 57.8 ± 8.1). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 (ASA 1 - 47; ASA II - 25; ASA III - 7). 3. Type of surgery: Not applicable (video-assisted thoracoscopic (VATS) lobectomy).
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: PCA - Fentanyl. sufentanil was inserted at 2 μg/hour. A bolus of 2 mL was allowed every 15 minutes up to a maximal dose of 10 μg/hour. Duration 48 hours postoperatively. Concurrent medication/care: All patients received flurbiprofen axetil 50 mg/day as baseline analgesic treatment unless

	contraindicated. In case of an analgesic failure (VAS score persistently > 4), tramadol was used as a rescue medication. . Indirectness: No indirectness Comments: Sufentanyl (n=49) Intervention 2: Continuous epidural - Fentanyl + Bupivacaine. Intraoperative: if there were no signs of intravascular or intrathecal administration, a 5–10 mL dose of ropivacaine 2.5 mg/mL (12.5–25 mg) was injected through the epidural catheter. Postoperative: When the surgery was completed, a solution of ropivacaine (0.15%) and sufentanil (0.2 μg/mL) was initiated in the Thoracic Epidural Analgesia group at a rate of 5–10 mL/hour (target: visual analogue scale [VAS] score < 4) with a bolus of 5 mL of the solution allowed every 40 minutes (patient-controlled epidural analgesia). Duration 48 hours postoperatively . Concurrent medication/care: All patients received flurbiprofen axetil 50 mg/day as baseline analgesic treatment unless contraindicated. In case of an analgesic failure (VAS score persistently > 4), tramadol was used as a rescue medication. Indirectness: No indirectness Comments: Sufentanil and Ropivacaine
Funding	Academic or government funding (supported by the Young Science Foundation of the Affiliated Hospital of Qingdao University.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCA versus EPIDURAL

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Complications - Other at postoperative to discharge; Group 1: 27/49, Group 2: 14/49; Comments: Includes atelectasis; subcutaneous emphysema; prolonged air leak; confusion; pneumonia
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome: Complications - Nausea at postoperative to discharge; Group 1: 16/49, Group 2: 5/49
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome: Complications - Vomiting at postoperative to discharge; Group 1: 8/49, Group 2: 0/49
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 2: Length of hospital stay
- Actual outcome: Length of stay at admission to discharge; median (IQR) days, Comments: PCA: 5.0 (4.0-8.5)
Epidural: 5.0 (3.5-7.0)
P value 0.94);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Appendix D: Forest plots

D.1 IV opioid versus oral opioid (immediate release)

Figure 86: Pain score <6 hours

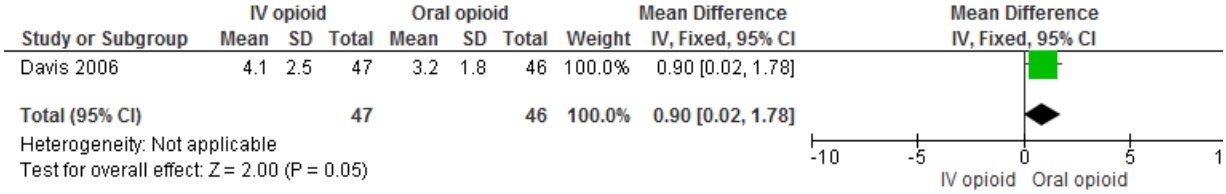


Figure 87: Pain score 6 - 24 hours

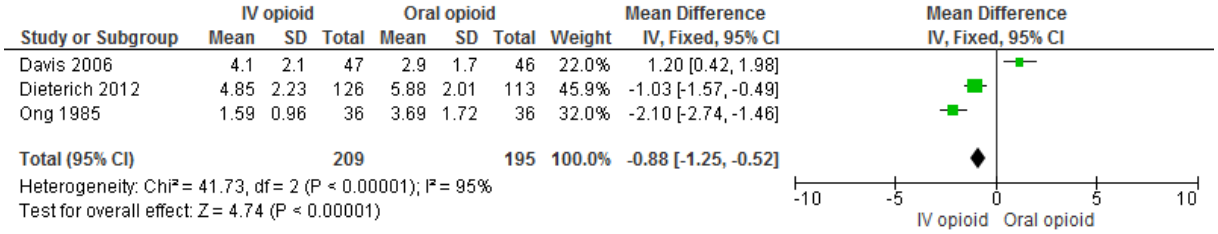


Figure 88: Pain score (Global assessment score) 6 -24 hours

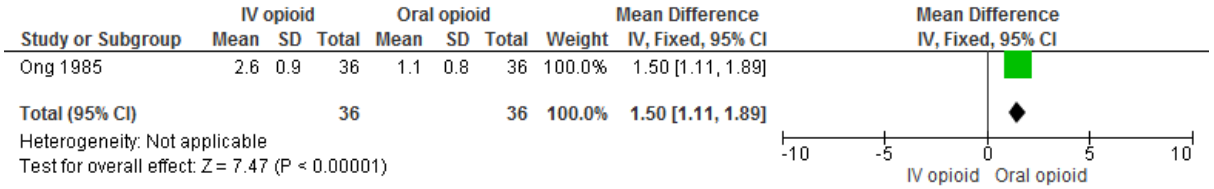


Figure 89: Adverse events (mean) at 6 hours

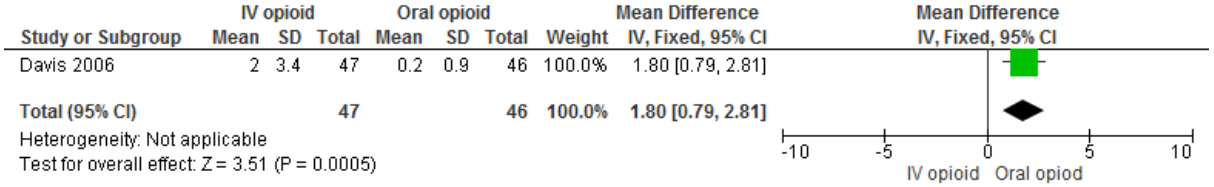


Figure 90: Adverse events (mean) at 24 hours

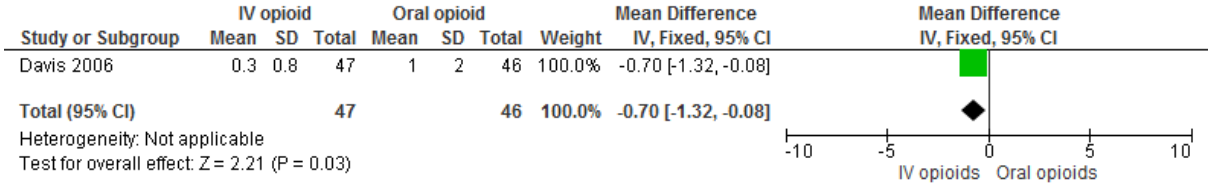


Figure 91: Adverse events

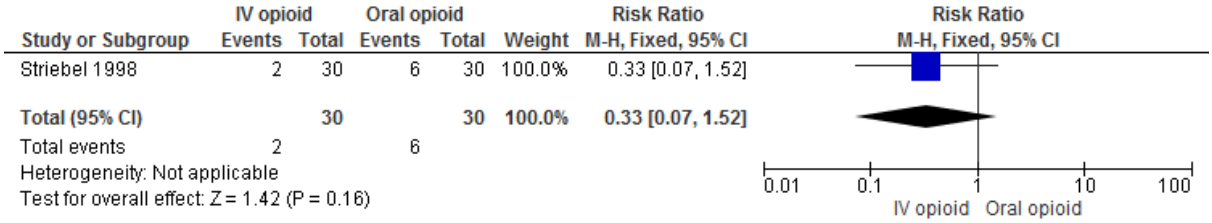


Figure 92: Hospital readmission

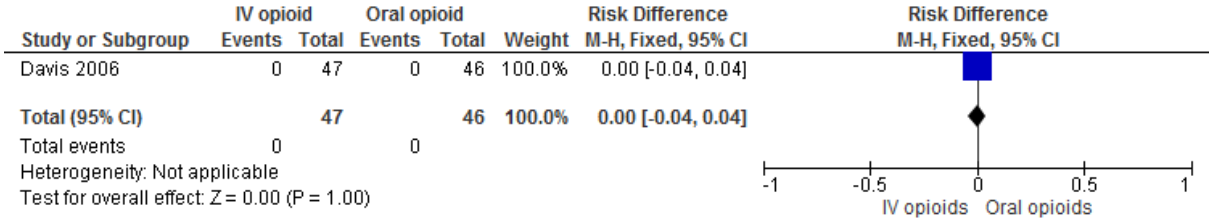


Figure 93: Additional medication (acetaminophen consumption) 6-24 hours

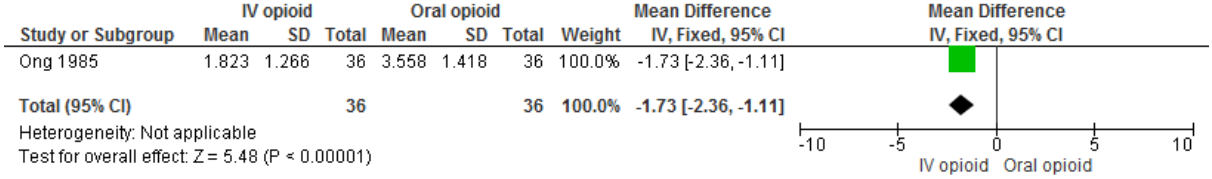
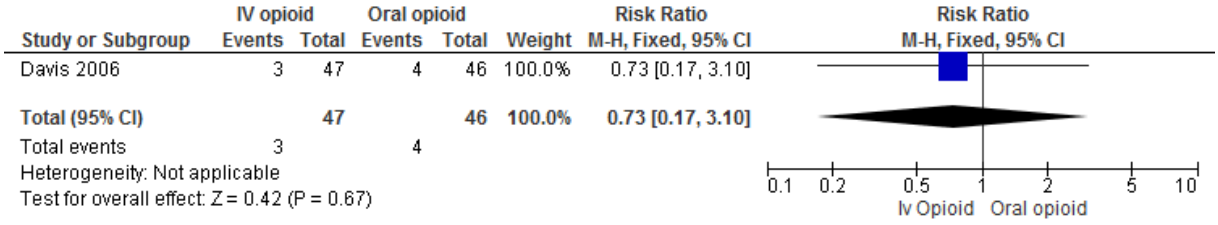


Figure 94: Amount of additional medication (number of people that needed additional medication)



D.2 IV opioid versus oral opioid (modified release)

Figure 95: Pain score (NRS) at 24 hours

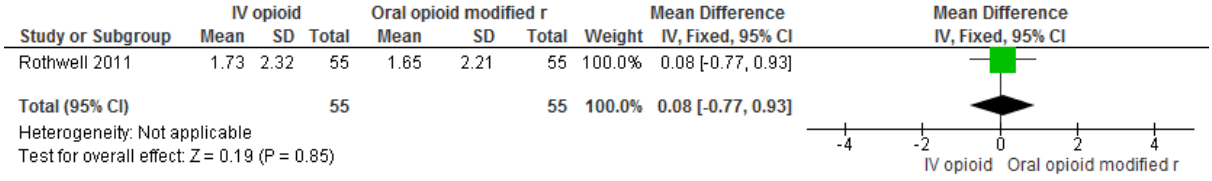
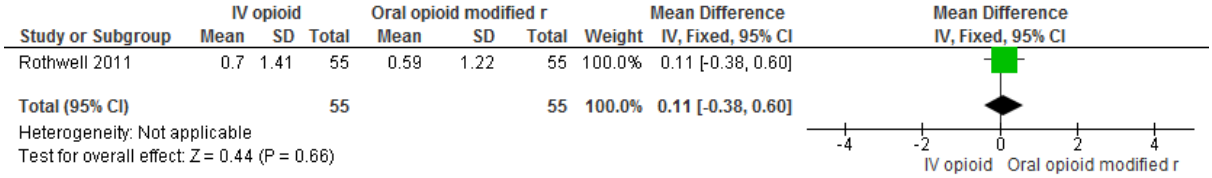
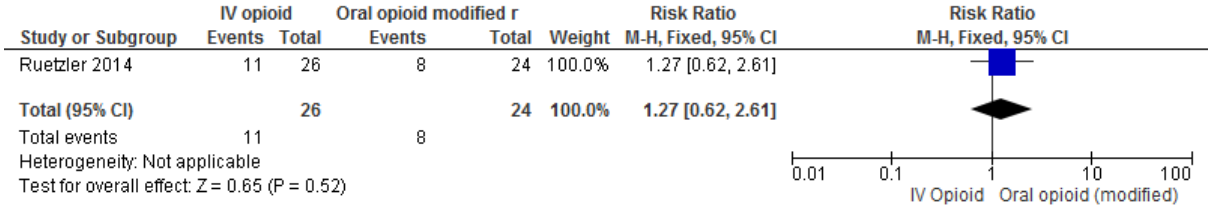


Figure 96: Adverse events (mean nausea score)



1

Figure 97: Adverse events (nausea vomiting)



2

D.3 PCA versus continuous epidural

Figure 98: Pain (VAS) at <6 hours

Study or Subgroup	PCA Mean	PCA SD	PCA Total	Continuous Mean	Continuous SD	Continuous Total	Weight	Mean Difference IV, Random, 95% CI
Bialka 2018	3.67	1.8	66	2	2	33	25.5%	1.67 [0.86, 2.48]
Rauck 1994	4.8	1.8	15	3.9	2.3	15	16.6%	0.90 [-0.58, 2.38]
Senturk 2002	3.2	1.4	23	2.8	1.6	22	24.5%	0.40 [-0.48, 1.28]
Tenenbein 2008	3.6	2.3	23	1.1	1.2	23	21.9%	2.50 [1.44, 3.56]
Wheatley 1990	3.1	2.846	10	0.6	1.5811	10	11.6%	2.50 [0.48, 4.52]
Total (95% CI)			**137**			**103**	**100.0%**	**1.51 [0.66, 2.36]**

Heterogeneity: Tau² = 0.57; Chi² = 11.09, df = 4 (P = 0.03); I² = 64%
Test for overall effect: Z = 3.48 (P = 0.0005)

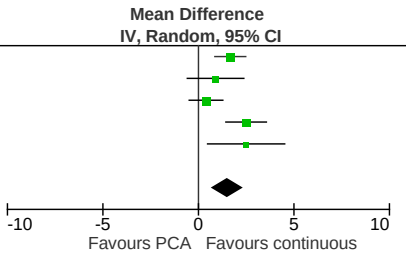


Figure 99: Pain (VAS) at 12 hours

Study or Subgroup	PCA Mean	PCA SD	PCA Total	Continuous Mean	Continuous SD	Continuous Total	Weight	Mean Difference IV, Fixed, 95% CI
Bialka 2018	3	1.6	66	2	2	33	31.5%	1.00 [0.22, 1.78]
Senturk 2002	2.4	1.1	23	1.4	0.9	22	56.3%	1.00 [0.41, 1.59]
Wheatley 1990	2.1	1.2649	10	1.4	1.5811	10	12.3%	0.70 [-0.55, 1.95]
Total (95% CI)			**99**			**65**	**100.0%**	**0.96 [0.52, 1.40]**

Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 4.29 (P < 0.0001)

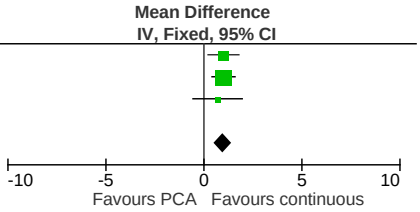


Figure 100: Pain (VAS) at 24 hours

Study or Subgroup	PCA Mean	PCA SD	PCA Total	Continuous Mean	Continuous SD	Continuous Total	Weight	Mean Difference IV, Random, 95% CI
Bialka 2018	3	1.6	66	2	2	33	13.5%	1.00 [0.22, 1.78]
Carli 2002	3.4	3.1	32	1.2	2.3	32	10.3%	2.20 [0.86, 3.54]
Owen 1993	2.1	0.4722	12	1.8	0.632	15	15.2%	0.30 [-0.12, 0.72]
Rauck 1994	3.7	2.1	15	0.03	0.05	15	11.9%	3.67 [2.61, 4.73]
Royse 2003	0.8	1.8	39	0.02	0.2	37	14.6%	0.78 [0.21, 1.35]
Senturk 2002	1.9	1	23	0.5	1.9	22	12.9%	1.40 [0.51, 2.29]
Tenenbein 2008	2.55	1.619	23	0.85	1.305	23	13.1%	1.70 [0.85, 2.55]
Wheatley 1990	1.2	1.5811	10	1.6	2.2136	10	8.6%	-0.40 [-2.09, 1.29]
Total (95% CI)			**220**			**187**	**100.0%**	**1.33 [0.60, 2.05]**

Heterogeneity: Tau² = 0.85; Chi² = 44.64, df = 7 (P < 0.00001); I² = 84%
Test for overall effect: Z = 3.60 (P = 0.0003)

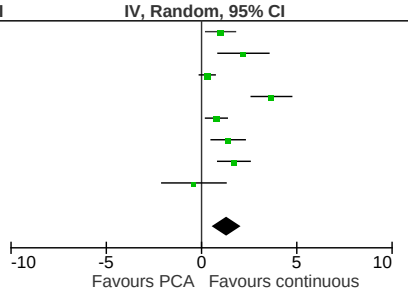


Figure 101: Pain (VAS) at 48 hours

Study or Subgroup	PCA Mean	PCA SD	PCA Total	Continuous Mean	Continuous SD	Continuous Total	Weight	Mean Difference IV, Random, 95% CI
Bialka 2018	2	1	66	1	1	33	16.2%	1.00 [0.58, 1.42]
Carli 2002	3.3	2.7	32	1.1	1.7	32	10.7%	2.20 [1.09, 3.31]
Owen 1993	1.06	0.2833	12	0.92	0.3973	15	17.1%	0.14 [-0.12, 0.40]
Rauck 1994	3.9	1.7	15	0.08	1.1	15	11.3%	3.82 [2.80, 4.84]
Royse 2003	1.2	2.7	39	0.1	0.4	37	12.7%	1.10 [0.24, 1.96]
Senturk 2002	1	0.4	23	0.2	0.4	22	17.2%	0.80 [0.57, 1.03]
Tenenbein 2008	1.25	1.226	23	0.4	0.771	23	14.9%	0.85 [0.26, 1.44]
Total (95% CI)			**210**			**177**	**100.0%**	**1.26 [0.68, 1.83]**

Heterogeneity: Tau² = 0.48; Chi² = 64.67, df = 6 (P < 0.00001); I² = 91%
Test for overall effect: Z = 4.30 (P < 0.0001)

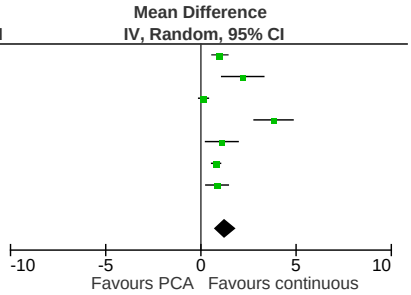


Figure 102: Pain relief (TOTPAR) at 24 hours

Study or Subgroup	PCA Mean	PCA SD	PCA Total	Continuous Mean	Continuous SD	Continuous Total	Weight	Mean Difference IV, Fixed, 95% CI
Benzon 1993	12.8	1.6	18	14.7	1.5	16	100.0%	-1.90 [-2.94, -0.86]
Total (95% CI)			**18**			**16**	**100.0%**	**-1.90 [-2.94, -0.86]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.57 (P = 0.0004)

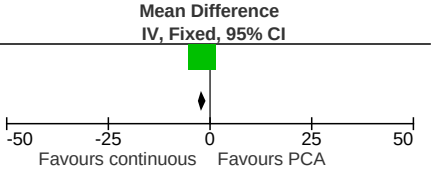


Figure 103: Pain relief (TOTPAR) at 48 hours

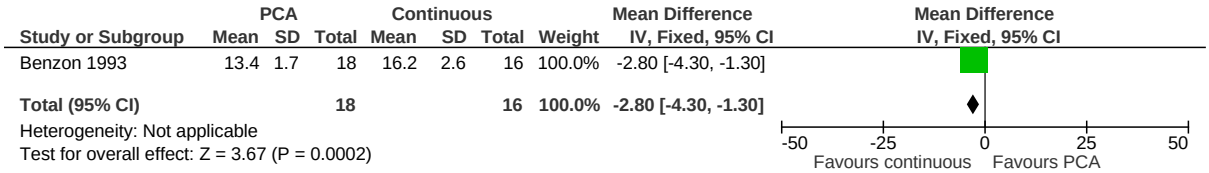


Figure 104: Total medication dose (morphine) at 48 hours

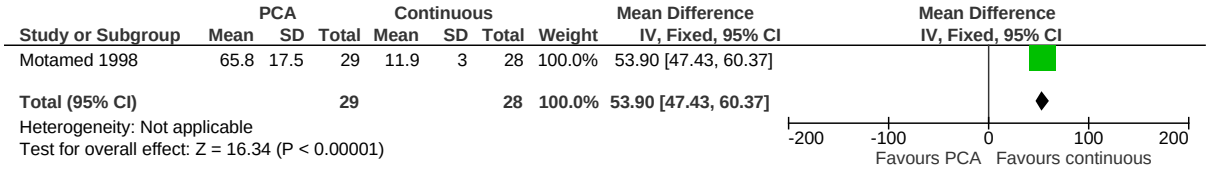


Figure 105: Depression

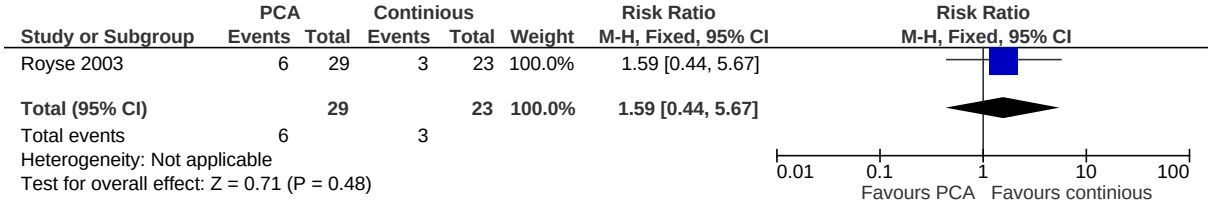


Figure 106: Post-traumatic stress

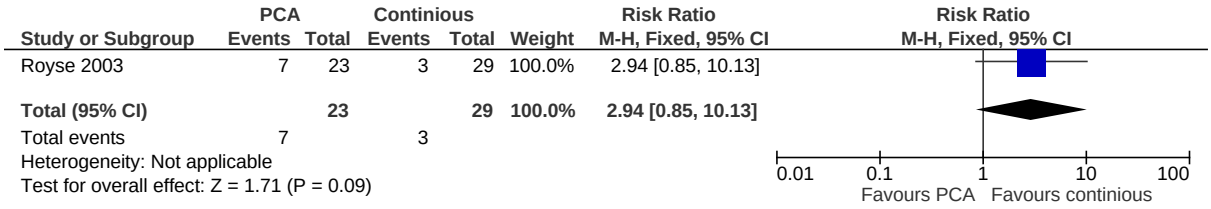


Figure 107: Complications: Nausea

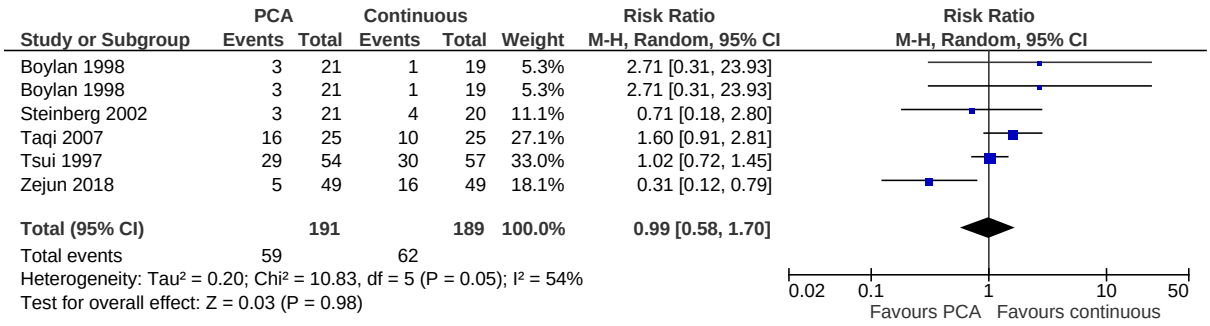


Figure 108: Complications: Vomiting

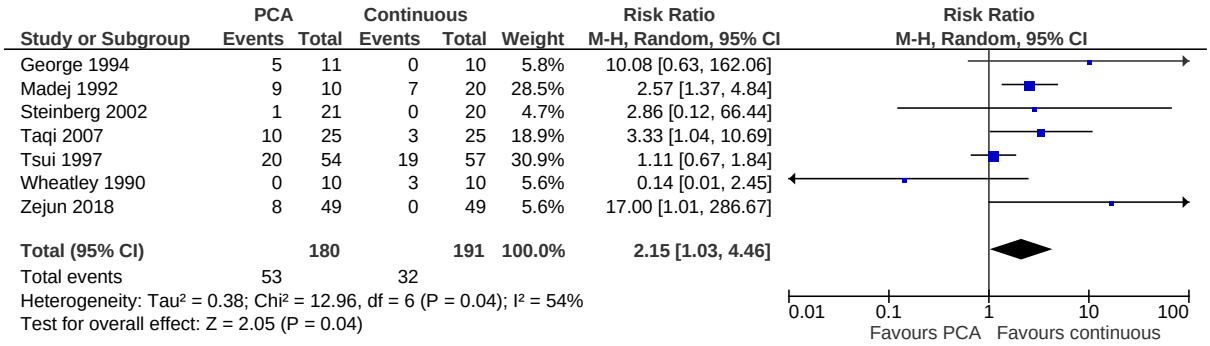


Figure 109: Complications: Nausea and vomiting

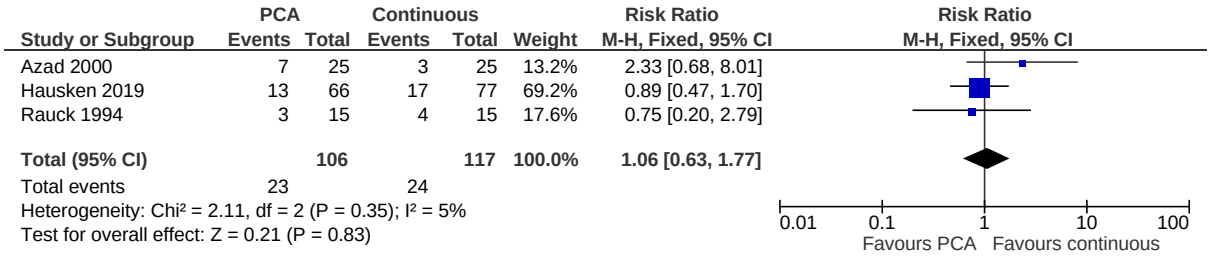


Figure 110: Complications: Respiratory depression

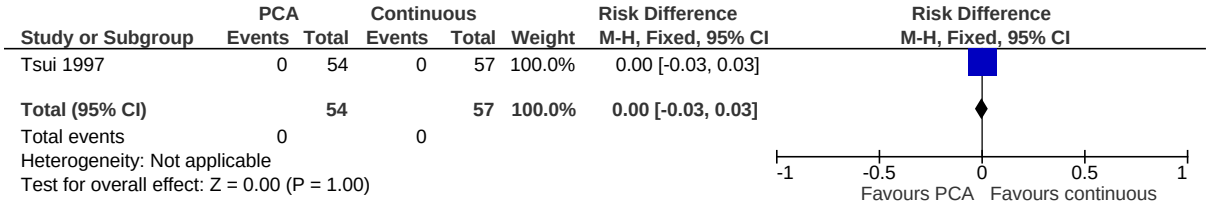


Figure 111: Functional measure: 6 minute walk test (meters walked in 6 minutes - difference from pre-op) at 3 weeks

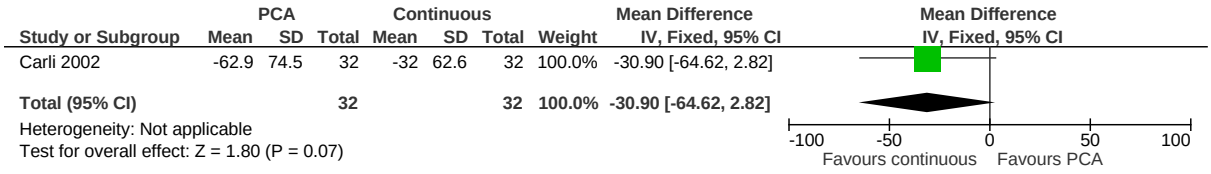


Figure 112: Functional measure: 6 minute walk test (meters walked in 6 minutes - difference from pre-op) at 6 weeks

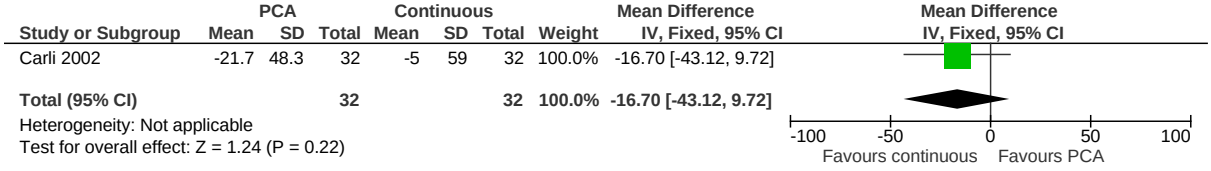


Figure 113: Length of hospital stay (days)

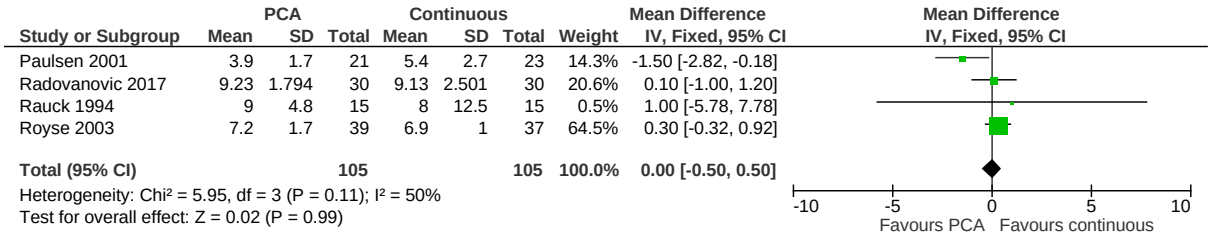


Figure 114: ICU length of stay (hours)

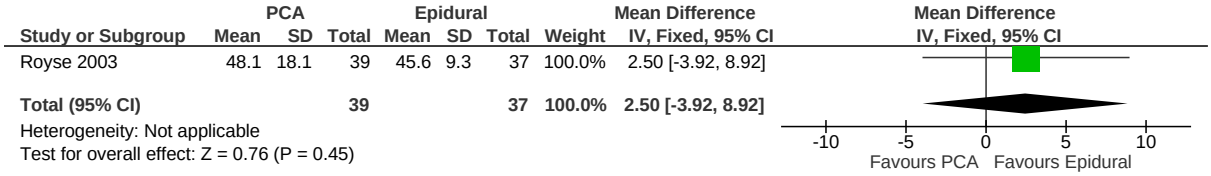
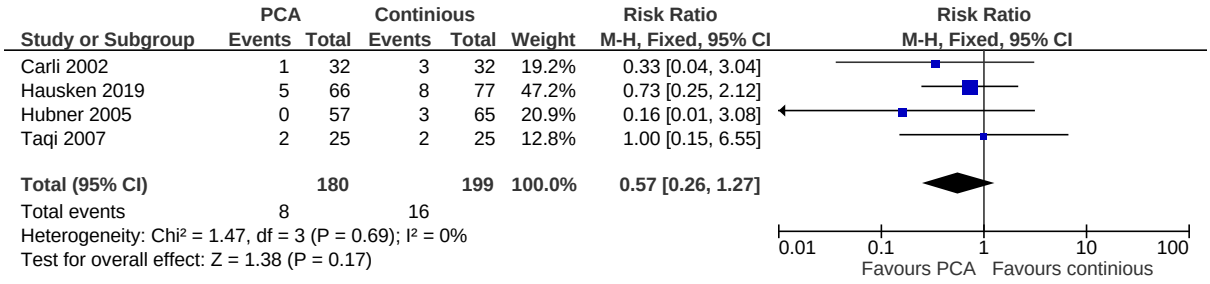


Figure 115: Hospital readmission



D.4 PCA versus spinal epidural

Figure 116: Hospital readmission

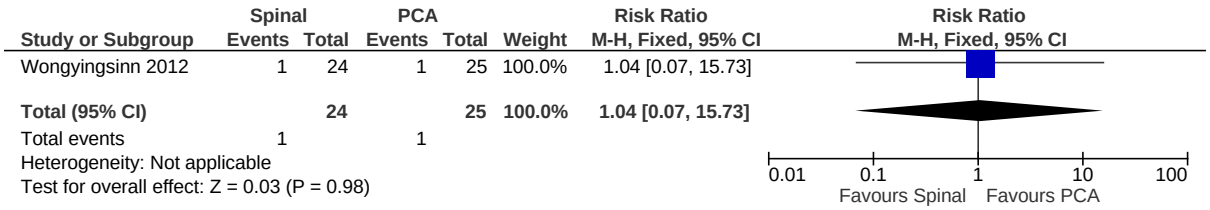


Figure 117: Complications: Nausea

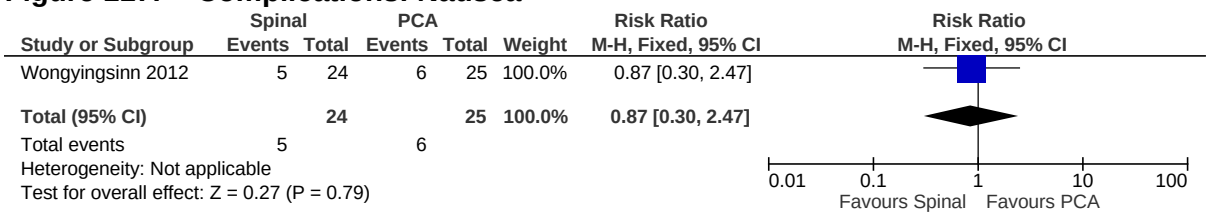


Figure 118: Complications: Vomiting

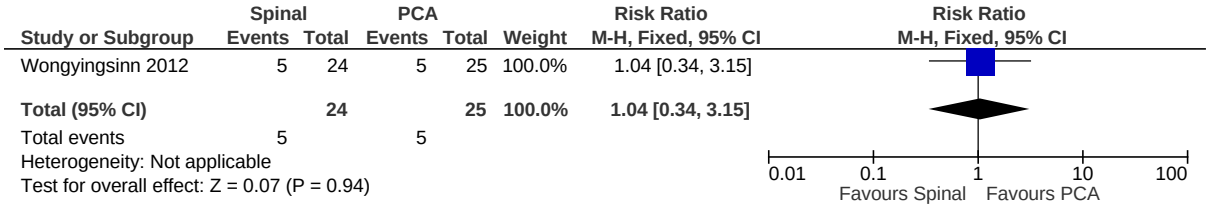


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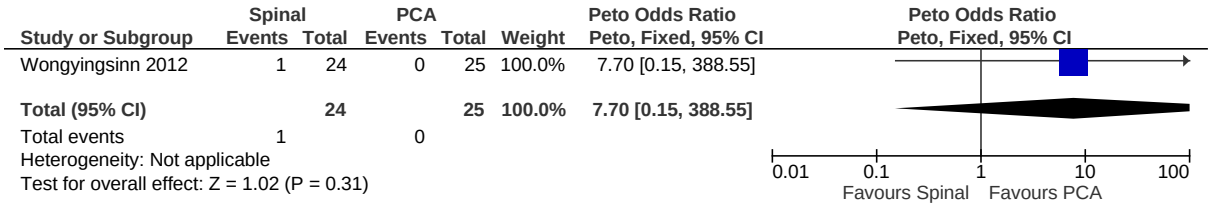
Figure 119: Complications: Respiratory depression



3 # D.5 Spinal epidural versus continuous epidural

Figure 120: Complications: Clavien dindo grade I

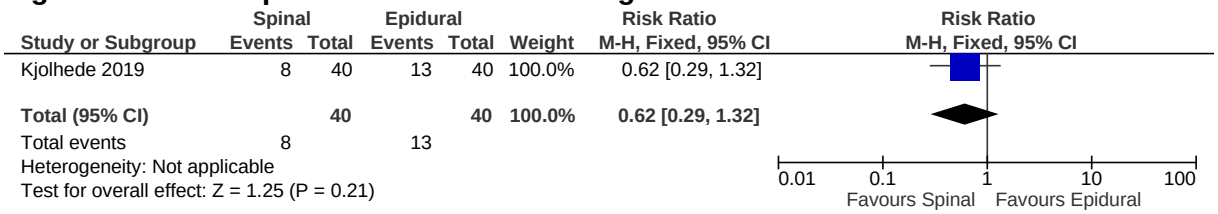


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Figure 121: Complications: Clavien dindo grade II

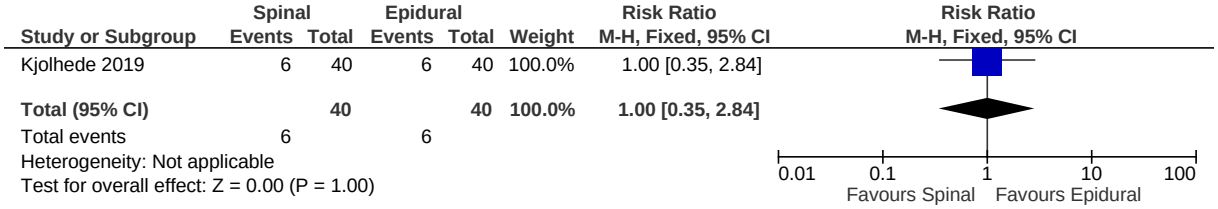

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Figure 122: Complications: Clavien dindo grade III

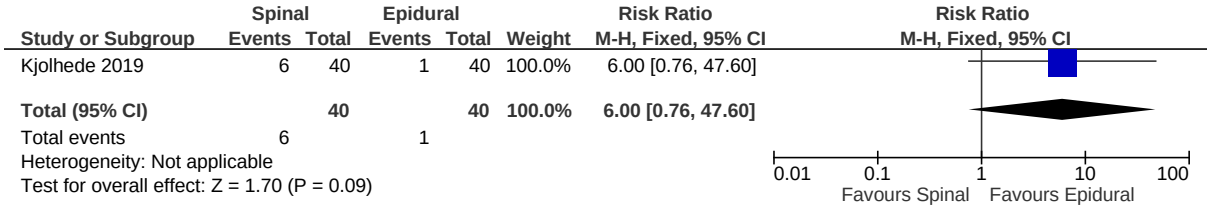

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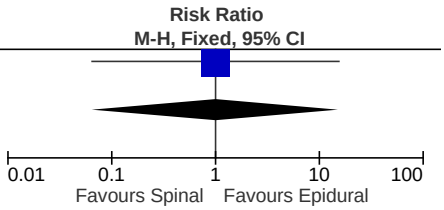
Figure 123: Complications: Clavien dindo grade IV

Study or Subgroup	Spinal Events	Spinal Total	Epidural Events	Epidural Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kjolhede 2019	1	40	1	40	100.0%	1.00 [0.06, 15.44]
Total (95% CI)		**40**		**40**	**100.0%**	**1.00 [0.06, 15.44]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



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Appendix E: GRADE tables

Table 26: Clinical evidence profile: IV opioid versus oral opioid (immediate release)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iv opioid versus oral opioid immediate release	Control	Relative (95% CI)	Absolute		
Pain (VAS) at >6 h (follow-up mean 6 hours; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	47	46	-	MD 0.9 higher (0.02 to 1.78 higher)	⊕OOO VERY LOW	CRITICAL
Pain (VAS) at 6-24 h (follow-up mean 6-24 Hours; Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	209	195	-	MD 0.88 lower (1.25 to 0.52 lower)	⊕OOO VERY LOW	CRITICAL
Pain (Global assessment score) 6-24 h (follow-up mean 8 hours; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	36	36	-	MD 1.5 higher (1.11 to 1.89 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (mean) at 6 hours (follow-up mean 0-6 Hours; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47	46	-	MD 1.8 higher (0.79 to 2.81 higher)	⊕⊕OO LOW	CRITICAL
Adverse events (mean)at 24 hours (follow-up mean 6-24 Hours; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	47	46	-	MD 0.7 lower (1.32 to 0.08 lower)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up mean 1 days)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	2/30 (6.7%)	20%	RR 0.33 (0.07 to 1.52)	134 fewer per 1000 (from 186 fewer to 104 more)	⊕OOO VERY LOW	CRITICAL
hospital readmission												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/47 (0%)	0%	Risk difference 0 (-0.04 to 0.04)	-	⊕OOO VERY LOW	IMPORTANT
additional medication (acetaminophen consumption)6-24 h (follow-up mean 8 hours; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision[2]	none	36	36	-	MD 1.73 lower (2.36 to 1.11 lower)	⊕⊕⊕O MODERATE	CRITICAL
Amount of additional medication (number of people) (follow-up mean 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/47 (6.4%)	8.7%	RR 0.73 (0.17 to 3.1)	23 fewer per 1000 (from 72 fewer to 183 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect Intervention

Table 27: Clinical evidence profile: IV opioid versus oral opioid (modified release)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV opioiod versus oral opioid modified release	Control	Relative (95% CI)	Absolute		
Pain (NRS) at 24 hours (follow-up mean 24 hours; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	55	55	-	MD 0.08 higher (0.77 lower to 0.93 higher)	⊕⊕OO LOW	CRITICAL
Adverse events (Mean Nausea score) (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	55	55	-	MD 0.11 higher (0.38 lower to 0.6 higher)	⊕OOO VERY LOW	CRITICAL
Adverse Events (Nausea, Vomiting) (follow-up mean 3 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/26 (42.3%)	33.3%	RR 1.27 (0.62 to 2.61)	90 more per 1000 (from 127 fewer to 536 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 28: Clinical evidence profile: PCA compared to continuous epidural for post-operative pain management

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCA	Continuous epidural	Relative (95% CI)	Absolute		
Pain: VAS (6 hours) (range of scores: 0-10; Better indicated by lower values)												
5	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[1]	none	152	120	-	MD 1.51 higher (0.66 to 2.36 higher)	⊕OOO VERY LOW	CRITICAL
Pain: VAS (12 hours) (range of scores: 0-10; Better indicated by lower values)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	99	65	-	MD 0.96 higher (0.52 to 1.4 higher)	⊕⊕OO LOW	CRITICAL
Pain: VAS (24 hours) (range of scores: 0-10; Better indicated by lower values)												
8	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[1]	none	378	348	-	MD 1.33 higher (0.60 to 2.05 higher)	⊕OOO VERY LOW	CRITICAL
Pain: VAS (48 hours) (range of scores: 0-10; Better indicated by lower values)												
7	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[1]	none	345	309	-	MD 1.26 higher (0.68 to 1.83 higher)	⊕OOO VERY LOW	CRITICAL
Pain reflief: TOTPAR (24 hours) (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18	16	-	MD 1.9 lower (2.94 to 0.86 lower)	⊕⊕⊕⊕ HIGH	
Pain relief: TOTPAR (48 hours) (Better indicated by higher values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18	16	-	MD 2.8 lower (4.3 to 1.3 lower)	⊕⊕⊕O MODERATE	CRITICAL
Total medication (Morphine) (follow-up mean 2 days; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	28	-	MD 53.9 higher (47.43 to 60.37 higher)	⊕⊕⊕O MODERATE	CRITICAL
Depression (follow-up 6 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/29 (20.7%)	13%	RR 1.59 (0.44 to 5.67)	77 more per 1000 (from 73 fewer to 607 more)	⊕⊕⊕O MODERATE	IMPORTANT
Post-traumatic Stress (follow-up 6 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	7/23 (30.4%)	10.3%	RR 2.94 (0.85 to 10.13)	200 more per 1000 (from 15 fewer to 940 more)	⊕⊕OO LOW	IMPORTANT
Complication - Nausea (follow-up post-operative period)												
6	randomised trials	serious[1]	serious[3]	no serious indirectness	very serious[1]	none	59/191 (30.9%)	32.8%	RR 0.99 (0.58 to 1.7)	3 fewer per 1000 (from 138 fewer to 230 more)	⊕OOO VERY LOW	IMPORTANT
Complication - Vomiting (follow-up post-operative period)												
7	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision[1]	none	53/180 (29.4%)	16.8%	RR 2.15 (1.03 to 4.46)	193 more per 1000 (from 5 more to 581 more)	⊕⊕OO LOW	IMPORTANT
Complication - Nausea and vomiting (follow-up post-operative period)												
3	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	very serious[1]	none	23/106 (21.7%)	20.5%	RR 1.06 (0.63 to 1.77)	12 more per 1000 (from 76 fewer to 158 more)	⊕OOO VERY LOW	CRITICAL

Complication - Respiratory depression (follow-up post-operative period)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/54 (0%)	0%	RD 0 (-0.03 to 0.03)	-	⊕⊕⊕O MODERATE	IMPORTANT
Functional measures - Distance walked in 6 minutes (follow-up 3 weeks; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 30.9 lower (64.62 lower to 2.82 higher)	⊕⊕OO LOW	IMPORTANT
Functional measures - Distance walked in 6 minutes (follow-up 6 weeks; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 16.7 lower (43.12 lower to 9.72 higher)	⊕⊕OO LOW	NOT IMPORTANT
Length of stay (Better indicated by lower values)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	163	161	-	MD 0 higher (0.5 lower to 0.5 higher)	⊕⊕⊕O MODERATE	IMPORTANT
ICU length of stay (Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	39	37	-	MD 2.5 higher (3.92 lower to 8.92 higher)	⊕⊕OO LOW	IMPORTANT
Hospital readmission (follow-up discharge to 30 days)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	8/180 (4.4%)	8%	RR 0.57 (0.26 to 1.27)	34 fewer per 1000 (from 59 fewer to 22 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 or 2 increments due to heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 29: Clinical evidence profile: PCA compared to spinal epidural for post-operative pain management

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCA	Spinal epidural	Relative (95% CI)	Absolute		
Readmission (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/24 (4.2%)	4%	RR 1.04 (0.07 to 15.73)	2 more per 1000 (from 37 fewer to 589 more)	⊕⊕OO LOW	IMPORTANT
Complication - Nausea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/24 (20.8%)	24%	RR 0.87 (0.3 to 2.47)	31 fewer per 1000 (from 168 fewer to 353 more)	⊕⊕OO LOW	IMPORTANT
Complication - Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/24 (20.8%)	20%	RR 1.04 (0.34 to 3.15)	8 more per 1000 (from 132 fewer to 430 more)	⊕⊕OO LOW	IMPORTANT
Complication - Respiratory depression												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/24 (4.2%)	0%	OR 7.7 (0.15 to 388.55)	-	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 30: Clinical evidence profile: Spinal epidural compared to continuous for post-operative pain management

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Spinal	Continuous	Relative	Absolute		

studies						considerations	epidural	epidural	(95% CI)			
complications (clavien dindo grade I) (follow-up 6 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency[1]	no serious indirectness	very serious[1]	none	8/40 (20%)	32.5%	RR 0.62 (0.29 to 1.32)	123 fewer per 1000 (from 231 fewer to 104 more)	⊕⊕OO LOW	CRITICAL
complications (clavien dindo grade II) (follow-up 6 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/40 (15%)	15%	RR 1 (0.35 to 2.84)	0 fewer per 1000 (from 98 fewer to 276 more)	⊕⊕OO LOW	CRITICAL
complications (clavien dindo grade III) (follow-up 6 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/40 (15%)	2.5%	RR 6 (0.76 to 47.6)	125 more per 1000 (from 6 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
complications (clavien dindo grade IV) (follow-up 6 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/40 (2.5%)	2.5%	RR 1 (0.06 to 15.44)	0 fewer per 1000 (from 24 fewer to 361 more)	⊕⊕OO LOW	CRITICAL

[1] · Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix F:Health economic evidence selection

The health economic study selection flow chart is shown in Figure 24.

Appendix G: Health economic evidence tables

None.

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 31: Studies excluded from the clinical review: IV versus oral opioid

Study	Exclusion reason
Banning 1986[73]	Incorrect interventions. modified release Vs Epidural
Bourke 2000[123]	Incorrect interventions. modified release Vs IM Morphine
Cheung 2017[168]	Inappropriate comparison. Incorrect interventions
Curtis 1999[210]	Inappropriate comparison
Desai 2017[239]	Incorrect interventions. Transdermal Buprenorphine Vs Oral Tramadol
Edwards 1999[260]	Inappropriate comparison. Incorrect interventions. SR for Aspirin
Flory 2001[298]	Incorrect interventions. Fixed Perocet schedule Vs PRN Perocet
Ginsberg 2003[335]	Incorrect interventions. Inappropriate comparison. IV oxycodone switched to Oral oxycodone
Houmes 1992[408]	Incorrect interventions. IV Tramadol Vs IV Morphine
Kaiko 1985[474]	Not review population. Inappropriate comparison. Incorrect interventions. Abstract only
Kaiko 1990[473]	Non-English language studies
Kampe 2009[483]	Incorrect interventions. Modifed Tramadol Vs Modified Oxycodone
Kay 1984[498]	Incorrect interventions. Controlled Morphine Vs Placebo
Konstantatos 2014[544]	Incorrect interventions. Oral oxycodone + Morphine PCA Vs Placebo + Morphine PCA
Kupers 1995[561]	Incorrect interventions. Oral tramadol vs Oral Pentazocine
Liu 2011[624]	Non-English language studies
Liu 2012[628]	Non-English language studies
Lund 1971[641]	Incorrect interventions. IV pethidine Vs IV Pentazocine
Manji 1997[660]	conference bastract
McDonnell 2010[689]	Incorrect interventions
McQuay 1986[695]	Incorrect interventions
Mhuircheartaigh 2009[718]	Incorrect interventions. A review of 5 studies, with incorrect interventions
NCT 2006[797]	citation only
Nct 2008[806]	Citation only
Nct 2008[808]	Citation only
Nct 2017[886]	Citation only
Nessim 1999[907]	Inappropriate comparison. Incorrect interventions
Oliver 2011[937]	Incorrect interventions. IV Morphine, Fentanyl and Propofol
Pandit 1986[967]	Not review population. IV Dezocine Vs IV Morphine
Pang 1999[968]	Incorrect interventions. IV tramadol Vs IV Fentanyl
Parbrook 1966[971]	Not review population. Incorrect interventions. IM Morphine Vs IM

	Methadone
Parikh 2013[974]	Incorrect interventions. Inappropriate comparison. Peritubal Ropivacaine Vs Ropivacaine + Morphine
Qi 2016[1022]	Incorrect interventions. IV Sulfentanil Vs IV Remifentanil
Rabinov 1987[1023]	Incorrect interventions
Rao 2001[1034]	No relevant outcomes
Rasmussen 2016[1039]	Incorrect interventions
Rawal 2001[1043]	Incorrect interventions. Tramadol Vs Paracetamol Vs Metamizole
Rawal 2006[1044]	Incorrect interventions. Subcutaneous local aneasthetic Vs Oral multimodal analgesia
Richards 2011[1059]	Inappropriate comparison
Richards 2013[1058]	Incorrect interventions. Combined oxycodone Morphine Vs Morphine Vs Oxycodone
Rundshagen 1998[1081]	Incorrect interventions
Saarnivaara 1980[1083]	Inappropriate comparison. Incorrect interventions. IM Pethidine vs IM Tilidine
Sadove 1973[1085]	Incorrect interventions. IM Myfadol Vs IM Meperidine
Scholz 2018[1113]	Inappropriate comparison
Schraag 1999[1114]	Incorrect study design. Comparative review of two different studies
Seymour 1983[1131]	Inappropriate comparison. Incorrect interventions
Shahbazi 2004[1135]	Incorrect interventions. IV morphine Vs IV sufentanil
Singla 2017[1164]	Incorrect interventions
Sloan 2008[1170]	Systematic review is not relevant to review question or unclear PICO
Stegmann 2008[1193]	Incorrect interventions
Stehling 1978[1194]	Incorrect interventions. Inappropriate comparison. IM administration of Butorphanol Vs Meperidine
Stoelting 1965[1200]	Incorrect interventions. IV Pentazocine Vs IV morphine
Striebel 1993[1203]	abstract only
Swerdlow 1964[1226]	Incorrect interventions. IV Phenazocine Vs IV Morphine
Tammisto 1971[1232]	Incorrect interventions. IV Pethidine Vs IV Pentazocine
Tarradell 1996[1245]	Incorrect interventions. Iv Tramadol vs IV meperidine
Tegon 2009[1249]	Incorrect interventions. Intervention - Soaked Opioid sponges
Tigerstedt 1981[1256]	Inappropriate comparison. Incorrect interventions. Study for Intracholedochal passage pressure
Twersky 2001[1281]	Incorrect interventions
Uluer 2012[1286]	Incorrect interventions. Intraoperative fentanyl Vs Remifentanil anaesthesia
Van Bergen 1960[1297]	Inappropriate comparison. Incorrect interventions
Van Steenberghe 1986[1308]	Inappropriate comparison. Incorrect interventions. Oral Ciramadol Vs oral codeine
Verschraegen 1979[1312]	Incorrect interventions
Vickers 1992[1313]	Incorrect interventions. Inappropriate comparison. PCA Pethidine Vs PCA Tramadol
Villesen 2007[1315]	Inappropriate comparison. Incorrect interventions

Vorsanger 2013[1322]	Incorrect interventions. Immediate release tapentadol Vs Oxycodone
Wade 2009[1323]	Inappropriate comparison. Incorrect interventions
Wang 2015[1329]	Inappropriate comparison. Incorrect interventions
Wang 2016[1333]	Incorrect interventions. PCA Oxycodone Vs PCA Sulfentanil
Waris 1994[1336]	Incorrect interventions
Watanabe 1982[1340]	Non-English language studies
Watanabe 1982[1339]	Non-English language studies
Welchew 1985[1346]	Inappropriate comparison. Incorrect interventions. PCA Pethidine Vs PCA Alfentanil
Wrench 1997[1365]	Not review population. Incorrect study design. Incorrect interventions. IV Pethidine Vs IV alfentanil
Xie 2017[1372]	Incorrect interventions. IV oxycodone vs IV fentanyl
Yanagida 1980[1385]	Non-English language studies
Yang 2016[1390]	Incorrect interventions. PCA + Fentanyl Vs PCA + Oxycodone
Yarmush 1997[1394]	Incorrect interventions. IV remifentanil Vs IV Morphine
Young 1977[1409]	Inappropriate comparison
Zacharias 1990[1420]	Incorrect interventions. Inappropriate comparison. PCA Vs IV Morphine
Zarauza 2000[1423]	Inappropriate comparison. Incorrect interventions. Nimodipine Vs Nifedipine
Zeedick 1979[1425]	Incorrect interventions. Oral butorphanol Vs oral codeine
Zelcer 1992[1429]	Inappropriate comparison. Incorrect interventions. IV Alfentanil Vs PCA Alfentanil
Zhou 2015[1439]	Inappropriate comparison. Incorrect interventions

Table 32: Studies excluded from the clinical review: opioid administration strategy

Reference	Reason for exclusion
Abd-Elsayed 2015[3]	Inappropriate intervention
Abuzaid 1993[8]	Inappropriate intervention
Aceto 2002[9]	Inappropriate intervention
Aguilar 1994[15]	Not in English
Albert 1988[27]	Inappropriate comparison
Alexander 1990[29]	Inappropriate comparison
Ali 2018[31]	Inappropriate intervention
Allaire 1992[34]	Inappropriate population
Alon 2003[35]	Inappropriate study design
Alonso Chico 2003[36]	Not in English
Amr 2010[39]	Inappropriate intervention
Andreoni 2002[41]	Inappropriate comparison
Araimo Morselli 2017[44]	Inappropriate comparison
Asantila 1991[51]	Inappropriate comparison
Atallah 2006[53]	Inappropriate comparison
Aydogan 2015[60]	Inappropriate comparison
Badner 1994[64]	Inappropriate comparison

Reference	Reason for exclusion
Badner 1992[65]	Inappropriate comparison
Bainbridge 2006[67]	Inappropriate intervention
Ballantyne 1993[70]	Systematic review references cross-checked
Barber 2002[74]	Inappropriate intervention
Barnes 1991[76]	Inappropriate comparison
Barratt 2002[77]	No relevant outcomes
Barzoi 2000[81]	Inappropriate comparison
Baubillier 1992[84]	Not in English
Baxter 1994[87]	Inappropriate intervention
Bedder 1991[89]	Inappropriate intervention
Bernard 1988[99]	Inappropriate comparison
Bernard 1993[100]	Inappropriate comparison
Bertini 2001[101]	Inappropriate comparison
Bertini 1995[102]	Not in English
Block 2003[109]	Inappropriate study design
Blumenthal 2005[111]	Inappropriate intervention
Blumenthal 2006[110]	Inappropriate population
Boezaart 1999[112]	Inappropriate comparison
Bogra 2005[113]	Inappropriate comparison
Bois 1997[114]	No relevant outcomes
Boldt 1998[115]	Inappropriate comparison
Bollish 1985[116]	Inappropriate comparison
Bonnal 2016[117]	Inappropriate intervention
Bouchard 1995[122]	Inappropriate comparison
Bowdle 1997[124]	Inappropriate study design
Braga Ade 2014[127]	Inappropriate comparison
Bredtmann 1991[128]	Paper not available
Briggs 1985[129]	Inappropriate comparison
Cadavid-Puentes 2017[138]	Not in English
Callesen 1999[140]	Inappropriate comparison
Campbell 2008[141]	Inappropriate comparison
Camu 1991[142]	Conference abstract
Capdevila 1999[145]	Inappropriate population
Caranza 1999[146]	Inappropriate comparison
Carli 2001[148]	Inappropriate comparison
Cassady 2000[150]	Inappropriate population
Chang 2004[155]	Inappropriate comparison
Chang 1991[157]	Not in English
Charghi 2003[160]	Inappropriate study design
Chauvin 1993[161]	No relevant outcomes
Chen 2011[164]	Systematic review references cross-checked
Chen 2015[165]	Inappropriate comparison
Chi 2017[170]	Inappropriate comparison
Cho 2017[172]	Inappropriate comparison
Choi 2003[175]	Inappropriate comparison

Reference	Reason for exclusion
Choi 2000[173]	Systematic review references cross-checked
Choi 2000[174]	Not in English
Choi 2003[176]	Not in English
Choi 2007[178]	Not in English
Choiniere [180]	Inappropriate comparison
Chrubasik 1996[184]	Inappropriate comparison
Chung 1997[186]	Not in English
Coe 1991[192]	Inappropriate comparison
Cohen 1998[195]	Inappropriate comparison
Cohen 1997[194]	Inappropriate population
Colwell Jr 1995[198]	Inappropriate comparison
Concha 2004[200]	Inappropriate comparison
Cooper 1995[201]	Inappropriate comparison
Cooper 1999[202]	Inappropriate comparison
Correll 2001[204]	Inappropriate population
Cottam 2007[205]	Inappropriate comparison
Cowan 2002[206]	Inappropriate comparison
Crisp 2012[207]	Inappropriate comparison
Cullen 1985[209]	Inappropriate comparison
Dahl 1988[213]	Inappropriate study design
Danieli 2012[216]	Inappropriate study design
Dawson 1995[223]	Inappropriate comparison
De Beer Jde 2005[224]	Inappropriate intervention
De Conno 1989[225]	Inappropriate comparison
De Leon-Casasola 1994[226]	Inappropriate study design
Della Rocca 2002[228]	Inappropriate comparison
Demirel 2014[229]	Inappropriate comparison
Demirkol Soyarslan 2009[232]	Not in English
Dichtwald 2017[241]	Inappropriate comparison
Dong 2018[250]	Systematic review references cross-checked
Duale 2003[253]	Inappropriate comparison
Dyer 1990[258]	Inappropriate comparison
Eaton 1997[259]	Inappropriate comparison
Egbert 1993[262]	Inappropriate comparison
Elkaradawy 2011[268]	No relevant outcomes
Ellis 1990[271]	Inappropriate intervention
Endoh 1996[274]	Not in English
Eriksson-Mjoberg 1997[277]	Inappropriate comparison
Eroglu 2006[278]	Inappropriate comparison
Eskander 1994[280]	Inappropriate comparison
Essving 2011[282]	Inappropriate comparison
Estanon-Garcia 2008[283]	Not in English
Fanshawe 1999[288]	Inappropriate intervention
Fant 2011[289]	Inappropriate comparison
Fassoulaki 2014[290]	Inappropriate comparison

Reference	Reason for exclusion
Fayed 2014[292]	Inappropriate comparison
Fischer 1988[296]	Inappropriate comparison
Flacke 1985[297]	Inappropriate comparison
Foss 2005[303]	Inappropriate comparison
Freire 2017[307]	Inappropriate comparison
Geller 1993[323]	Inappropriate intervention
George 1994[324]	Inappropriate comparison
Ghee 2018[328]	Inappropriate comparison
Gherghina 2010[329]	Retracted paper
Gong 2003[337]	Not in English
Gopinathan 2000[339]	Inappropriate comparison
Graham 1995[345]	Inappropriate comparison
Graham 1997[346]	Inappropriate comparison
Grant 1990[348]	Inappropriate comparison
Grant 1993[347]	Inappropriate comparison
Green 2007[349]	Inappropriate comparison
Guay 2016[351]	Systematic review references cross-checked
Guinard 1992[354]	Inappropriate intervention
Gulucu 2009[355]	Not in English
Gunjan 2016[356]	Inappropriate comparison
Gupta 2003[357]	Inappropriate comparison
Gupta 2006[358]	Inappropriate population
Gurlit 2004[361]	Inappropriate comparison
Hakan Erbay 2010[369]	Inappropriate comparison
Hakobyan 2008[370]	Inappropriate study design
Hallworth 1997[372]	Conference abstract
Han 2001[376]	Not in English
Hancke 2013[378]	Not in English
Hansdottir 2006[381]	Inappropriate comparison
Harukuni 1995[383]	Inappropriate comparison
Hecker 1988[388]	Inappropriate comparison
Hege-Scheuing 1995[391]	Not in English
Hering 1997[395]	Not in English
Ho 1998[401]	Inappropriate study design
Holmstrom 1993[402]	Inappropriate population
Hopkins 1998[405]	Inappropriate comparison
Hotta 2011[407]	Inappropriate comparison
Howell 1995[409]	Inappropriate comparison
Hu 2009[410]	Not in English
Huang 1990[413]	Not in English
Hudcova 2006[416]	Systematic review references cross-checked
Hudcova 2005[415]	Retracted paper
Husaini 1998[419]	Inappropriate comparison
Husegaard 1984[420]	Not in English
Hutchins 2018[421]	Inappropriate comparison

Reference	Reason for exclusion
Hwang 2014[422]	Inappropriate comparison
Hwang 1997[423]	Not in English
Idowu 2011[426]	Inappropriate intervention
Inan 2007[428]	Inappropriate comparison
Jacobson 1989[434]	Inappropriate comparison
Jarraya 2016[440]	Inappropriate comparison
Jayr 1993[443]	Inappropriate intervention
Jayr 1998[442]	Inappropriate intervention
Jeon 2011[449]	Inappropriate comparison
Johnson 1989[456]	Inappropriate intervention
Jorgensen 2000[461]	Inappropriate comparison
Jørgensen 2001[460]	Inappropriate comparison
Joris 2003[462]	Inappropriate comparison
Joshi 1995[465]	Inappropriate population
Jung 2016[469]	Inappropriate comparison
Kahn 1999[472]	Inappropriate comparison
Kainzwaldner 2013[475]	Not in English
Kakehata 2000[476]	Not in English
Kaloul 2004[478]	Inappropriate intervention
Kammoun 2008[480]	Not in English
Kampe 2002[481]	Inappropriate comparison
Kampe 2001[482]	No relevant outcomes
Kang 2009[484]	Not in English
Kararmaz 2004[489]	Not in English
Kati 2005[495]	Inappropriate comparison
Kati 2001[494]	Not in English
Kentner 1996[500]	Not in English
Khalili 2012[503]	Not in English
Kikuchi 2018[510]	Protocol only
Kim 2006[521]	Inappropriate comparison
Kim 2016[514]	Inappropriate comparison
Kim 2009[517]	Inappropriate comparison
Kim 1999[512]	Not in English
Kim 2015[522]	Inappropriate comparison
Kim 2017[523]	Inappropriate comparison
Kim 2015[524]	Inappropriate comparison
Kiya 2003[530]	Not in English
Klasen 1999[533]	Inappropriate comparison
Klatt 2013[535]	Inappropriate population
Kluba 2010[536]	Inappropriate population
Konishi 1995[542]	Not in English
Kontrimaviciute 2012[545]	Inappropriate comparison
Kossmann 1983[547]	Not in English
Kostamovaara 2001[549]	Inappropriate intervention
Kowalski 1992[552]	Unavailable abstract

Reference	Reason for exclusion
Kroon 2010[554]	Inappropriate comparison
Kumar 2017[558]	Inappropriate comparison
Kwon 2016[564]	Inappropriate comparison
Lam 1994[569]	Inappropriate comparison
Lane 2005[570]	Inappropriate comparison
Lattermann 2007[573]	No relevant outcomes
Lebovits 2001[579]	Inappropriate comparison
Lee 1991[582]	Inappropriate intervention
Lee 2016[594]	Inappropriate comparison
Lee 1988[583]	Inappropriate comparison
Lee 1995[584]	Not in English
Lee 2001[593]	Not in English
Lee 2014[590]	Inappropriate comparison
Lena 2003[596]	Inappropriate comparison
Lenz 2009[598]	Inappropriate comparison
Levy 2010[604]	Systematic review references cross-checked
Lew 2004[605]	Inappropriate comparison
Li 2016[611]	Inappropriate comparison
Lim 2006[615]	Inappropriate intervention
Limberi 2003[616]	Inappropriate intervention
Liu 2001[622]	Inappropriate comparison
Liu 1995[625]	Inappropriate comparison
Liu 2015[631]	Not in English
Liu 2019[623]	Systematic review references cross-checked
Loane 2012[633]	Inappropriate intervention
Logas 1987[635]	Inappropriate comparison
Loper 1990[637]	Inappropriate intervention
Lorenzini 2002[638]	Inappropriate comparison
Lubenow 1996[640]	Inappropriate intervention
Lutti 2000[645]	Inappropriate comparison
Ma 2005[646]	Not in English
Macias 2002[650]	Inappropriate study design
Madi-Jebara 2005[653]	Not in English
Mahoney 1990[654]	Inappropriate comparison
Mangano 1992[659]	Inappropriate comparison
Mann 2000[661]	Inappropriate comparison
Mannion 2005[662]	Inappropriate intervention
Marappa 2017[667]	Inappropriate comparison
Marret 2007[672]	Systematic review references cross-checked
Massicotte 2009[676]	Inappropriate intervention
Matsunaga 1984[684]	Not in English
Maurer 2003[685]	Inappropriate intervention
Mayo 2003[687]	Not in English
McNicol 2015[692]	Systematic review references cross-checked
Mehta 1999[699]	Inappropriate comparison

Reference	Reason for exclusion
Meng 2017[703]	Systematic review references cross-checked
Menigaux 2001[707]	Inappropriate comparison
Mercadante 2008[709]	Inappropriate intervention
Mercanoglu 2013[710]	Inappropriate intervention
Mercieri 2017[711]	Inappropriate comparison
Messina 2009[713]	Inappropriate intervention
Mezei 2002[717]	Not in English
Mima 1969[722]	Not in English
Mishra 2018[723]	Inappropriate intervention
Misiran 2013[726]	Inappropriate comparison
Mitsuhata 1993[728]	Not in English
Mitsuhata 1994[729]	Not in English
Mitsuhata 1991[730]	Not in English
Modi 2009[733]	Inappropriate intervention
Modig 1981[734]	Inappropriate comparison
Mohamad 2017[736]	Inappropriate comparison
Mondor 2010[742]	Inappropriate comparison
Morad 2012[751]	Inappropriate intervention
Morad 2009[752]	Inappropriate intervention
Moradi-Farsani 2018[753]	Not in English
Moreira 2014[754]	Inappropriate comparison
Morgan 2006[755]	Inappropriate comparison
Moskovitz 1986[760]	Inappropriate comparison
Moslemi 2015[761]	Inappropriate comparison
Mostafa 2018[762]	Inappropriate intervention
Mota 2010[763]	Inappropriate comparison
Motamed 1998[764]	Conference abstract
Mourisse 1992[768]	Inappropriate comparison
Movafegh 2007[769]	Inappropriate comparison
Mozell 1991[771]	Inappropriate intervention
Mukherjee 2010[774]	Inappropriate comparison
Mukherjee 2012[773]	Inappropriate intervention
Murakami 2009[776]	Not in English
Murouchi 2016[778]	Inappropriate intervention
Murphy 1994[779]	Inappropriate intervention
Nag 1984[782]	Inappropriate comparison
Navas 1996[789]	Not in English
NCT 2017[891]	Citation only
NCT 2017[897]	Citation only
NCT 2016[873]	Citation only
NCT 2016[875]	Citation only
NCT 2016[884]	Citation only
NCT 2016[876]	Citation only
NCT 2016[882]	Citation only
NCT 2016[872]	Citation only

Reference	Reason for exclusion
NCT 2015[870]	Citation only
NCT 2014[860]	Citation only
NCT 2014[854]	Citation only
NCT 2013[852]	Citation only
NCT 2013[849]	Citation only
NCT 2013[851]	Citation only
NCT 2012[843]	Citation only
NCT 2012[844]	Citation only
NCT 2012[847]	Citation only
NCT 2011[842]	Citation only
NCT 2011[838]	Citation only
NCT 2009[827]	Citation only
NCT 2008[807]	Citation only
NCT 2008[820]	Citation only
NCT 2008[805]	Citation only
NCT 2006[794]	Citation only
NCT 2006[796]	Citation only
NCT 2006[795]	Citation only
NCT 2005[791]	Citation only
Nendick 2000[902]	Inappropriate intervention
Neudecker 1999[908]	Inappropriate comparison
Ng 1990[914]	Not in English
Ngan Kee 1997[915]	Inappropriate comparison
Nie 2017[917]	Inappropriate comparison
Nielsen 1989[918]	Inappropriate intervention
Niemi 1994[920]	Inappropriate intervention
Nightingale 2007[922]	Inappropriate intervention
Nilsson 1997[923]	Inappropriate comparison
Nolan 1992[927]	Inappropriate intervention
O'Halloran 1997[929]	Inappropriate intervention
O'Hara 2004[930]	Inappropriate population
Oifa 2009[934]	Inappropriate comparison
Okajima 2015[935]	Inappropriate intervention
Oliashirazi 2017[936]	Inappropriate comparison
Onal 2007[944]	Not in English
Ong 2010[947]	Inappropriate comparison
Owen 1989[949]	Inappropriate comparison
Ozcan 2003[950]	Not in English
Oztekin 2006[953]	Inappropriate comparison
Öztürk 2016[954]	Not in English
Paech 1989[956]	Inappropriate comparison
Palacios 1991[959]	Inappropriate comparison
Pan 1994[960]	Inappropriate comparison
Pan 1994[961]	Inappropriate intervention
Park 1999[977]	Not in English

Reference	Reason for exclusion
Park 2006[982]	Not in English
Park 2011[975]	Inappropriate study design
Park 2016[980]	Inappropriate comparison
Parker 1991[983]	Inappropriate comparison
Parker 1992[984]	Inappropriate intervention
Patrick 1991[988]	Inappropriate intervention
Pavlidis 2002[991]	Inappropriate intervention
Pettersson 2000[999]	Inappropriate intervention
Peyton 2003[1001]	Inappropriate information available
Phaphak 2003[1002]	Not in English
Phillips 1984[1003]	Inappropriate comparison
Pintaric 2011[1006]	Inappropriate intervention
Poon 2009[1010]	Inappropriate comparison
Popping 2008[1011]	Systematic review references cross-checked
Popping 2012[1012]	Inappropriate comparison
Poyhia 2004[1014]	Inappropriate comparison
Prasartritha 2010[1016]	Inappropriate intervention
Priestley 2002[1017]	Inappropriate intervention
Prieto-Alvarez 2002[1018]	Inappropriate comparison
Radpay 2003[1026]	Inappropriate comparison
Rawal 1997[1046]	Systematic review is not relevant to review question.
Rawal 1999[1042]	Inappropriate study design
Richardson 2009[1060]	Systematic review references cross-checked
Rimaitis 2006[1061]	Inappropriate information available
Roediger 2006[1064]	Inappropriate intervention
Rosaeg 1994[1069]	Inappropriate intervention
Rosseel 1988[1070]	Inappropriate comparison
Roussier 2006[1072]	No relevant outcomes
Rud 2015[1078]	Not in English
Rudra 1991[1079]	Inappropriate comparison
Saari 2014[1082]	No relevant outcomes
Saffer 2015[1088]	Inappropriate intervention
Sagiroglu 2013[1089]	Not in English
Sakai 2003[1094]	Inappropriate comparison
Salicath 2018[1095]	Systematic review references cross-checked
Sandler 1992[1101]	No relevant outcomes
Sandler 1986[1100]	Inappropriate comparison
Sarmiento-Ramirez 2007[1103]	Not in English
Sarvela 2002[1105]	Inappropriate intervention
Satomi 2018[1106]	Inappropriate intervention
Sawchuk 1993[1109]	Inappropriate intervention
Scarfe 2016[1110]	Systematic review references cross-checked
Schnabel 2010[1112]	Systematic review references cross-checked
Schulze 1988[1115]	No relevant outcomes
Schumann 2003[1116]	No relevant outcomes

Reference	Reason for exclusion
Scott 1996[1117]	Inappropriate intervention
Senagore 2003[1125]	Inappropriate comparison
Seo 2016[1130]	No relevant outcomes
Shao 2010[1136]	Not in English
Sharar 1991[1137]	Inappropriate intervention
Shi 2014[1138]	Systematic review references cross-checked
Shulman 1984[1139]	Inappropriate intervention
Sidebotham 1997[1142]	Not in English
Sierra 1995[1144]	Not in English
Silvasti 2000[1148]	Inappropriate intervention
Silvasti 2001[1149]	Inappropriate population
Sinatra 1991[1151]	Inappropriate intervention
Sindhvananda 2004[1152]	Inappropriate outcomes
Singelyn 1999[1155]	Inappropriate study design
Singelyn 1998[1153]	Inappropriate population
Singelyn 2005[1154]	Inappropriate population
Singh 2015[1158]	Inappropriate intervention
Singh 2009[1160]	Inappropriate
Singh 2016[1156]	Inappropriate comparison
Singh 2001[1159]	Inappropriate intervention
Singhal 2006[1161]	Inappropriate intervention
Slinger 1995[1169]	Inappropriate intervention
Smith 1991[1173]	Inappropriate intervention
Sng 2016[1175]	Inappropriate intervention
Spence 1970[1183]	Inappropriate study design
St. Peter 2012[1189]	Inappropriate population
Stamenkovic 2008[1190]	Inappropriate intervention
Staren 1986[1191]	Inappropriate study design
Stenseth 1996[1197]	No relevant outcomes
Stevens 1993[1198]	Inappropriate comparison
Stoddart 1993[1199]	No relevant outcomes
Sultan 2016[1211]	Inappropriate comparison
Sumida 2009[1212]	Systematic review references cross-checked
Sviggum 2016[1223]	Inappropriate comparison
Swaroop 2002[1224]	Inappropriate intervention
Swenson 1994[1225]	Inappropriate intervention
Takahashi 2005[1229]	Not in English
Takenaka-Hamaya 2002[1230]	Inappropriate intervention
Tan 1997[1234]	Inappropriate study design
Tan 2003[1233]	Inappropriate intervention
Tanaka 1993[1237]	Inappropriate comparison
Tanaka 1991[1238]	Inappropriate comparison
Taverne 1992[1247]	Inappropriate intervention
Tenopala Villegas 1999[1252]	Not in English
Thomson 1995[1254]	Inappropriate intervention

Reference	Reason for exclusion
Thongrong 2011[1255]	Inappropriate intervention
Toussaint 2000[1264]	Inappropriate comparison
Tsang 1999[1266]	No relevant outcomes
Tuman 1991[1270]	Inappropriate information available
Tunc 2002[1271]	Not in English
Tuncel 2005[1273]	Inappropriate intervention
Turunen 2009[1279]	Inappropriate intervention
Unlugenc 2008[1289]	Inappropriate comparison
Urban 2002[1290]	Inappropriate comparison
Vaghadia 1997[1293]	Inappropriate comparison
Valairucha 2005[1296]	Inappropriate comparison
van den Nieuwenhuyzen 1996[1299]	Inappropriate comparison
van den Nieuwenhuyzen 1995[1300]	Inappropriate intervention
van den Nieuwenhuyzen 1998[1301]	Inappropriate comparison
Van der Auwera 1987[1302]	No relevant outcomes
van Lersberghe 1994[1307]	Inappropriate comparison
Verborgh 1988[1310]	Inappropriate intervention
Vickers 1995[1314]	Inappropriate intervention
Viscusi 2009[1319]	Inappropriate comparison
von Ungern-Sternberg 2005[1320]	Inappropriate study design
Vora 2012[1321]	Inappropriate intervention
Walder 2001[1325]	Systematic review references cross-checked
Wang 2009[1327]	Not in English
Wang 2006[1332]	Inappropriate intervention
Welchew 1991[1345]	Inappropriate intervention
Weller 1991[1347]	Inappropriate population
Werawatganon 2013[1348]	Study withdrawn
Werawatganon 2008[1349]	Systematic review references cross-checked
White 1992[1352]	Inappropriate comparison
White 2012[1351]	Inappropriate intervention
Wilde 1988[1356]	Inappropriate comparison
Winter 2007[1358]	Systematic review references cross-checked
Wittels 1993[1359]	Inappropriate comparison
Wolff 1986[1360]	Inappropriate comparison
Wu 2005[1366]	Inappropriate intervention
Wu 2016[1368]	Inappropriate comparison
Wuethrich 2015[1369]	Inappropriate study design
Wulf 1999[1370]	Inappropriate intervention
Xue 2000[1375]	Not in English
Yaddanapudi 2000[1377]	Inappropriate study design
Yanagidate 2004[1386]	Inappropriate comparison
Yang 1993[1391]	Inappropriate intervention

Reference	Reason for exclusion
Yardeni 2007[1393]	Inappropriate comparison
Yarnell 1992[1395]	Inappropriate intervention
Yavuz 2004[1396]	Inappropriate intervention
Yeung 2016[1402]	Systematic review references cross-checked
Yilmaz 2007[1403]	Not in English
Yokota 2000[1404]	Inappropriate comparison
Yonemura 1990[1405]	Not in English
Yoon 2007[1406]	Not in English
Yosunkaya 2003[1408]	No relevant outcomes
Youssef 2014[1412]	Systematic review references cross-checked
Ypsilantis 2010[1413]	Systematic review references cross-checked
Yu 1997[1416]	Not in English
Zeid 2012[1426]	Inappropriate intervention
Zotou 2014[1446]	Inappropriate intervention
Zucker 1998[1447]	Inappropriate intervention
Zutshi 2005[1448]	Inappropriate information available

H.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 33: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Intravenous ketamine

Appendix A: Review protocol

Table 34: Review protocol: Managing acute postoperative pain: IV ketamine

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	What is the most clinically and cost effective strategy for managing acute postoperative pain?
2.	Review question	What is the most clinically and cost effective strategy for managing acute postoperative pain? There are six topic areas that have been identified: Paracetamol routes of delivery Non-steroidal anti-inflammatory drugs (NSAIDs) Opioid administration strategy (Continuous epidural ,intravenous PCA, spinal) Opioid post-operative administration strategy (oral vs iv) Ketamine Neuropathic nerve stabilisers This protocol addresses, 'What is the clinical and cost effectiveness of adding IV ketamine to IV opioids in managing acute post-operative pain ?'
3.	Objective	To determine if adding iv ketamine to iv opioids is clinically and cost effective in managing acute post-operative pain.
4.	Searches	The following databases will be searched: • Embase • MEDLINE • The Cochrane Library Searches will be restricted by: • English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being	What is the most clinically and cost effective

	studied	strategy for managing acute postoperative pain
6.	Population	Inclusion: Adults (18 years and older) who have undergone surgery. Exclusion: People who have had Surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	IV ketamine and IV opioid
8.	Comparator/Reference standard/Confounding factors	IV opioids (and placebo)
9.	Types of study to be included	Randomised controlled trials and systematic reviews of randomised controlled trials
10.	Other exclusion criteria	Non-English language Cross-over randomised controlled trials
11.	Context	NA

12.	Primary outcomes (critical outcomes)	• Health-related quality of life
		• Pain reduction
		  ○ < 6 hours post op
		  ○ 6 hours- 24 hours post op
		Pain reduction measured by:
		  • patient reported pain (physician, nurse or carer reported pain will not be included);
		  • patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both)
		  • patient reported pain intensity expressed hourly over four to six hours using validated pain scales, or reported summed pain intensity difference (SPID) at four to six hours
		  • Number of participants achieving at least 50% pain relief
		  • Time to achieve 50% pain intensity
		• Amount of additional medication use (rescue medication)
		  ○ < 6 hours post op
		  ○ 6 hours- 24 hours post op
		• Time to rescue medication
		• Adverse events (including respiratory depression, nausea, vomiting)

13.	Secondary outcomes (important outcomes)	• Psychological distress and mental well-being • Symptom scores • Functional measures • Length of stay in intensive care

		• Length of stay in hospital • Hospital readmission The committee agreed that a difference of 1 (10%) on a 10 point pain scale such as NRS or VRS indicated a clinically important difference. For the remaining outcomes, the committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Cochrane RoB (2.0) will be used to assess intervention reviews 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management The clinical approach to this area of the scope is multimodal. The pain management approach for each patient will depend on many factors and include the procedure and the severity of

		pain. For this reason it is not meaningful to compare the drugs listed in the topic areas to each other. There isn't an overall question evaluating which drug is the most effective and a network meta-analysis is not appropriate.	
17.	Analysis of sub-groups	Subgroups: • people aged over 60 years • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation • American Society of Anesthesiologists (ASA) Physical Status grade • Opioid tolerant populations • High dose (>0.5mg/kg IV) and low dose (0.1 – 0.5mg/kg IV)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	NA	
22.	Anticipated completion date	NA	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☑
		Piloting of the study selection process	☐ / ☑
		Formal screening of search results against eligibility criteria	☐ / ☑
		Data extraction	☐ / ☑
		Risk of bias (quality) assessment	☐ / ☑
		Data analysis	☐ / ☑
24.	Named contact	5a. Named contact National Guideline Centre	

		5b Named contact e-mail perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swaine Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis Ms Lina Gulhane
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.

29.	Other registration details	NA	
30.	Reference/URL for published protocol	NA	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • Issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Perioperative care Pain relief Paracetamol	
33.	Details of existing review of same topic by same authors	NA	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	NA	
36.	Details of final publication	www.nice.org.uk	

1

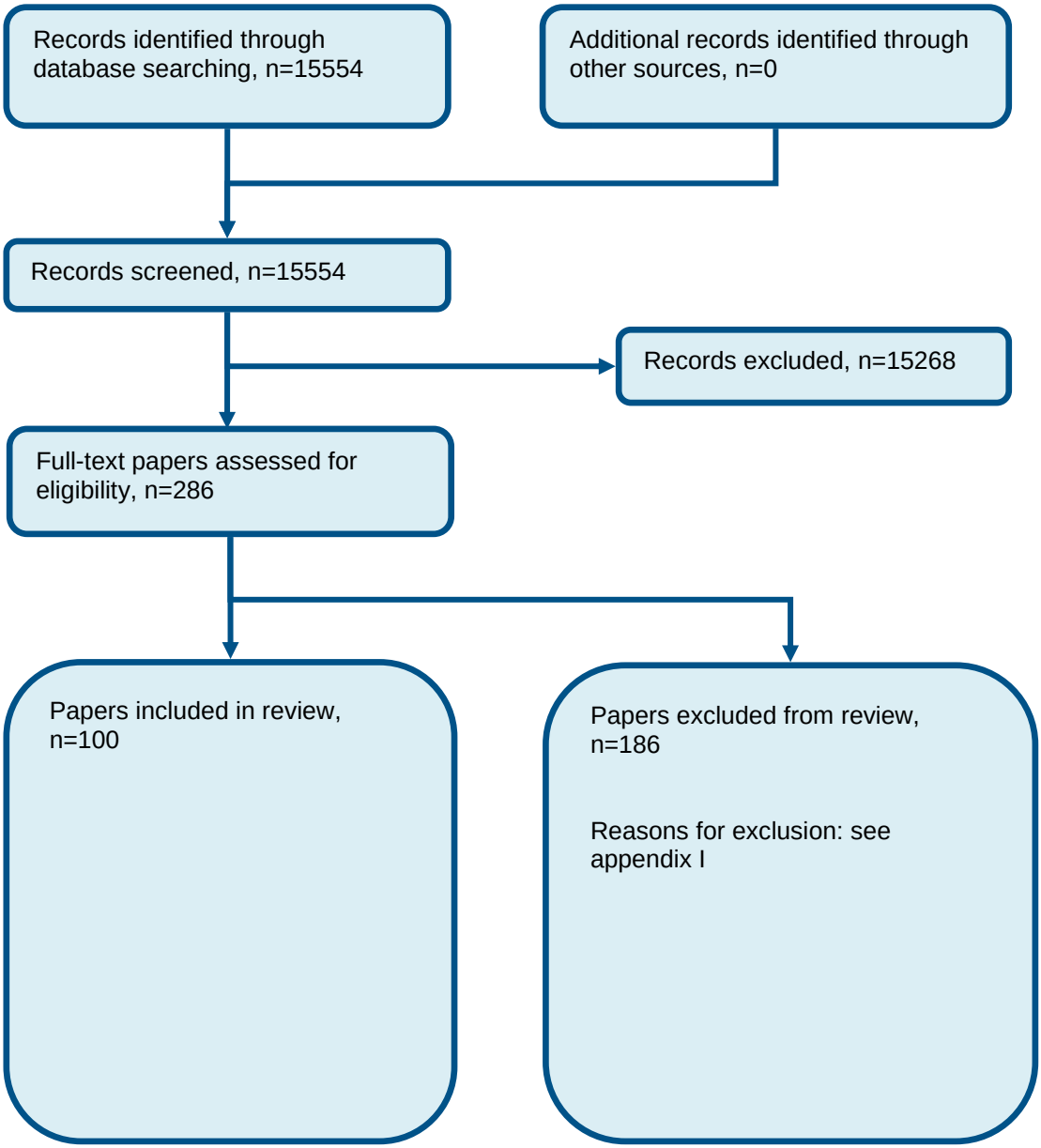
2

3 The health economic review protocol is shown in

4 Table **3**.

Appendix B: Clinical evidence selection

Figure 124: Flow chart of clinical study selection for the review of IV ketamine



Appendix C: Clinical evidence tables

Study	Unlugenc 2002[1287]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in Turkey; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	66 ASA Physical status 1 or 2 patients, between the ages of 18 and 59 years, scheduled for elective major abdominal surgery with general anaesthesia were recruited.
Exclusion criteria	Inability to use PCA, long term use of opioid medications, and history of chronic pain
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Tramadol-ketamine - 48(4); Tramadol - 47(2). Gender (M:F): 26/17. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (Major abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA Tramadol 5mg/ml + ketamine 1 mg/ml. In all groups 4 mg odansetron and and 0.4 mg/kg meperidine were prescribed intravenously every 4 hours as rescue antiemetic and analgesic respectively. Duration post op. Concurrent medication/care: All patients were premedicated with intravenous midazolam 0.1 mg/kg 60 min before operation. anesthesia was induced with thiopenthal sodium (5mg/kg) and maintained with 1.5-2 % sevoflurane in a mixture of 66% nitrous oxide and 34 % oxygen. Indirectness: No indirectness (n=21) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA Tramadol 5 mg/ml. In all groups 4 mg odansetron and and 0.4 mg/kg meperidine were prescribed intravenously every 4 hours as rescue antiemetic and analgesic respectively. Duration post op. Concurrent medication/care: All patients were premedicated with intravenous midazolam 0.1 mg/kg 60 min before operation. anesthesia was induced with thiopenthal sodium (5mg/kg) and maintained with 1.5-2 % sevoflurane in a mixture of 66% nitrous oxide and

Study	Unlugenc 2002[1287]
	34 % oxygen. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS at 6 hours at 6 hours; Median (range)
tramadol+ketamine - 2(1-3); tramadol 2 (1-3);
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VRS at 24hours at 24 hours; Median (range)
tramadol+ketamine - 1(1-2); tramadol 1 (1-2);
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Mean Bolus PCA Tramadol doses (mg) 6 hours at 6 hours; Group 1: mean 55 mg (SD 43); n=22, Group 2: mean 120 mg (SD 47); n=21
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Mean Bolus PCA Tramadol doses (mg) 24 hours at 24 hours; Group 1: mean 70 mg (SD 89); n=22, Group 2: mean 180 mg (SD 32); n=21
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: total PCA Tramadol doses (mg) 6 hours at 6 hours; Group 1: mean 280 mg (SD 44); n=22, Group 2: mean 405 mg (SD 51); n=21
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: total PCA Tramadol doses (mg) 24 hours at 24 hours; Group 1: mean 850 mg (SD 56); n=22, Group 2: mean 975 mg (SD 31); n=21
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at 24 hours; Group 1: 6/22, Group 2: 9/21
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Unlugenc 2002[1287]
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Yalcin 2012[1382]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Turkey; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	enrolled 90 patients of ASA physical status I-II scheduled for elective total abdominal hysterectomy
Exclusion criteria	Patients with a history of psychiatric disorders, chronic pain, renal, cardiac orhematological insufficiency, chronic analgesic or opioid treatment, age dbelow 35 yr and above 70 yr, inability to use a patient-controlled analgesia(PCA) device and duration of surgery over 120 min were excluded from the study
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine group - 48.26(5.66); control group 48.14(5.98). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (Hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients in Ketamine group received intravenous (iv) bolus ketamine 0.5 mg/kg, before the induction of anesthesia. The patients in ketamine group also received a maintenance infusion of5 µg/kg/min ketamine intraoperatively until skin

Study	Yalcin 2012[1382]
	closure. When VAS score was less than 5, patients were connected to a PCA device set to deliver 1mg morphine as an iv bolus with a 6-min lockout interval; continuous infusionwas not allowed. This PCA regimen was continued for 48 hrs. Duration intra+48 h post op. Concurrent medication/care: All patients were premedicated with 10 mg oral diazepam the night before surgery and 10 mg intramuscular diazepam one hour before surgery.General anesthesia was induced with remifentanil 1 µg/kg and propofol 1.5-2 mg /kg followed by atracurium 0.5mg/kg to facilitate tracheal intubation. Anesthesia was maintained with 0.4 µg/kg/minremifentanil infusion and desflurane 0.5 MAC.. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients in controlgroup received physiologic saline; beforethe induction of anesthesia. When VAS score was less than 5, patients wereconnected to a PCA device set to deliver 1 mg morphine as an iv bolus with a6-min lockout interval; continuous infusion was not allowed. This PCA regimenwas continued for 48 hrs. Duration intra+48 h post op. Concurrent medication/care: All patients were premedicated with 10 mg oral diazepam the night before surgery and 10 mg intramuscular diazepam one hour before surgery.General anesthesia was induced with remifentanil 1 µg/kg and propofol 1.5-2 mg /kg followed by atracurium 0.5mg/kg to facilitate tracheal intubation. Anesthesia was maintained with 0.4 µg/kg/minremifentanil infusion and desflurane 0.5 MAC.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain VAS at 6 hours post op at 6 hours post op; reported in the graph
ketamine~2; control~2.5;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3
- Actual outcome: Pain VAS at 24 hours post op at 24 hours post op; reported in the graph
ketamine~0; control~0.25;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: morphine (PCA) consumption 6 hours post op at 6 hours post op; Group 1: mean 23.53 (SD 8.96); n=26, Group 2: mean 36.7 (SD 7.16); n=27

Study	Yalcin 2012[1382]
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3 - Actual outcome: morphine (PCA) consumption 24 hours post op at 24 hours post op; Group 1: mean 35.34 (SD 13.71); n=26, Group 2: mean 73.03 (SD 22.41); n=27 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Snijdelaar 2004[1176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Canada; Setting: department of anesthesia
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Inclusion criteria were ability to speak dutch, 17 18 years of age, ASA class1-3, stable or no significant central nervous system, respiratory cardiac, hepatic, renal or endocrine dysfunction and/or endocrine dysfunction and/or any significant sequelae. body weight 60-100 kg with a body mass index =< 30kgm^{-2}
Exclusion criteria	history significant psychopathology, chronic pain or chronic use of opioid analgesics, previous allergies or adverse reactions to opiod analgesics, ingestion of antitussive medication (dextromethorphan) within 48 hours of surgery, history of alcohol or drug dependency or abuse.
Recruitment/selection of patients	not specified

Study	Snijdelaar 2004[1176]
Age, gender and ethnicity	Age - Mean (SD): Ketamine/morphine. Gender (M:F): all male. Ethnicity: not stated
Further population details	1. Age: Not stated / Unclear 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1-3). 3. Type of surgery: urology (prostatectomy).
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. The PCA system was programmed to deliver a bolus of 0.5 ml, corresponding to a bolus dose of 0.5 mg s(+)-ketamine plus 1 mg of morphine for the ketamine/morphine group . Duration post op. Concurrent medication/care: Premedication consisted of oral midazolam 7.5 mg(administered 45–60 min before the expectedtime of induction of general anaesthesia). An additional 2 mg midazolam was given intravenously after insertion of a venousline. Five minutes before induction with propofol(2 mg.kg)1) and fentanyl (2 lg.kg)1), patients received a bolus injection of 0.1 ml.kg)1 s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group),followed by a continuous infusion of 0.002 ml.kg)1.min)1of the same agent. For patients in the ketamine/morphine group,this amounted to a bolus dose of 100 lg.kg)1 s(+)-ketamine and a continuous infusion of 2 lg.kg)1.min)1s(+)-ketamine. After induction, 0.6 mg.kg)1 rocuroniumwas given to facilitate tracheal intubation. Anaesthesia was maintained with isoflurane inN2O/O2 (60%/40%) aiming at an end expiratory concentration of isoflurane of 0.7%.Further rocuronium 0.1–0.2 mg.kg)1 was given when necessary. Morphine in a dose of 50 lg.kg)1 was given when there were signs of inadequate analgesia (increase in blood pressure or heart rate above 10% of baseline value). The continuous infusion of s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group) was stopped at skin closure. At the conclusion of surgery,neuromuscular blockade was reversed (when necessary) with neostigmine (0.05 mg.kg)1) and atropine (0.01–0.02 mg.kg)1).

Study	Snijdelaar 2004[1176]
	. Indirectness: No indirectness (n=14) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. The PCA system was programmed to deliver a bolus of 0.5 ml, corresponding to 1 mg morphine for the saline/morphine group.. Duration post op. Concurrent medication/care: Premedication consisted of oral midazolam 7.5 mg(administered 45–60 min before the expectedtime of induction of general anaesthesia). An additional 2 mg midazolam was given intravenously after insertion of a venousline. Five minutes before induction with propofol(2 mg.kg)1) and fentanyl (2 lg.kg)1), patients received a bolus injection of 0.1 ml.kg)1 s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group),followed by a continuous infusion of 0.002 ml.kg)1.min)1of the same agent. For patients in the ketamine/morphine group,this amounted to a bolus dose of 100 lg.kg)1 s(+)-ketamine and a continuous infusion of 2 lg.kg)1.min)1s(+)-ketamine. After induction, 0.6 mg.kg)1 rocuroniumwas given to facilitate tracheal intubation. Anaesthesia was maintained with isoflurane inN2O/O2 (60%/40%) aiming at an end expiratory concentration of isoflurane of 0.7%.Further rocuronium 0.1–0.2 mg.kg)1 was given when necessary. Morphine in a dose of 50 lg.kg)1 was given when there were signs of inadequate analgesia (increase in blood pressure or heart rate above 10% of baseline value). The continuous infusion of s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group) was stopped at skin closure. At the conclusion of surgery,neuromuscular blockade was reversed (when necessary) with neostigmine (0.05 mg.kg)1) and atropine (0.01–0.02 mg.kg)1). . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain VAS at 4 hours at 4 hours post op; Group 1: mean 1.4 (SD 1.2); n=13, Group 2: mean 2.9 (SD 1.6); n=12 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 - Actual outcome: Pain VAS at 24 hours at 24 hours post op; Group 1: mean 1.2 (SD 1); n=13, Group 2: mean 2 (SD 1.4); n=12 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2	

Study	Snijdelaar 2004[1176]
Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: cumulative post op PCA morphine consumption at post op; Group 1: mean 47.9 (SD 26.2); n=13, Group 2: mean 73.4 (SD 34.8); n=12 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: nausea 24 h post op at 24 h post op; Group 1: mean 1.1 (SD 2.1); n=13, Group 2: mean 0.4 (SD 0.6); n=12 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 - Actual outcome: nausea 48 h post op at 48 h post op; Group 1: mean 0.1 (SD 0.4); n=13, Group 2: mean 0.4 (SD 1); n=12 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 - Actual outcome: vomiting 24 h post op at 24 h post op; Group 1: 0/13, Group 2: 1/11 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 - Actual outcome: vomiting 48 h post op at 48 h post op; Group 1: 0/13, Group 2: 1/11 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Hadi 2013[367]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Hungary; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline	Adequate method of assessment/diagnosis

Study	Hadi 2013[367]
condition	
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Inclusion criterion was that the patient was adult who had a level of education which enabled him to understand the use of the patient-controlled analgesia technique. Those patients who had used bed rest and had physical therapy sessions by licensed physical therapists to relieve their lower back pain at least 48 h prior to surgery were included in the trial.
Exclusion criteria	Exclusion criteria were that patients with severe back pain who were receiving chronic narcotic analgesic treatment were excluded, as were patients with major systemic diseases.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Periop 55(2.6); intra 69(2.6); CTRL 71(2.6). Gender (M:F): 21/24. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (microdiscectomy surgery).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Peri group - ketamine (1 µg/kg/min) both intra- and postoperatively. Duration 24 hours. Concurrent medication/care: All patients were given midazolam 0.25 mg/kg orally, 30 min before surgery as a premedication. On arrival at the operating theater, the following drugs were given: propofol 2 mg/kg as an IV bolus for induction in all the three groups followed by atracurium 0.6 mg/kg to facilitate orotracheal intubation. Sevoflurane (1–1.5% v/v) in a carrier gas mixture of 1:1 nitorus oxide/oxygen was used for all patients. Anesthesia was pre-induced using remifentanil 1 lg/kg for the three groups followed by a remifentanil infusion at a dose of 0.2 lg/kg/min. A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 lg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 lg/kg/min administered using two different cannulas. All drugs were stopped at the end of the operation except for G3 where the ketamine was continued to be administered at 1 lg/kg/min for 24 h

Study	Hadi 2013[367]
	. Indirectness: No indirectness (n=15) Intervention 2: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Intra group - ketamine(1 µg/kg/min) intra-operatively. Duration 24 hours. Concurrent medication/care: All patients were given midazolam 0.25 mg/kg orally, 30 min before surgery as a premedication. On arrival at the operating theater, the following drugs were given: propofol 2 mg/kg as an IV bolus for induction in all the three groups followed by atracurium 0.6 mg/kg to facilitate orotracheal intubation. Sevoflurane (1–1.5% v/v) in a carrier gas mixture of 1:1 nitorus oxide/oxygen was used for all patients. Anesthesia was pre-induced using remifentanil 1 lg/kg for the three groups followed by a remifentanil infusion at a dose of 0.2 lg/kg/min. A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 lg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 lg/kg/min administered using two different cannulas. All drugs were stopped at the end of the operation except for G3 where the ketamine was continued to be administered at 1 lg/kg/min for 24 h. Indirectness: No indirectness (n=15) Intervention 3: Opioid (IV) and placebo - Opioid + placebo. Control group - received normal saline, A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 µg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 µg/kg/min administered using two different cannulas. . Duration 24 hours. Concurrent medication/care: All patients were given midazolam 0.25 mg/kg orally, 30 min before surgery as a premedication. On arrival at the operating theater, the following drugs were given: propofol 2 mg/kg as an IV bolus for induction in all the three groups followed by atracurium 0.6 mg/kg to facilitate orotracheal intubation. Sevoflurane (1–1.5% v/v) in a carrier gas mixture of 1:1 nitorus oxide/oxygen

Study	Hadi 2013[367]
	was used for all patients. Anesthesia was pre-induced using remifentanil 1 lg/kg for the three groups followed by a remifentanil infusion at a dose of 0.2 lg/kg/min. A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 lg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 lg/kg/min administered using two different cannulas. All drugs were stopped at the end of the operation except for G3 where the ketamine was continued to be administered at 1 lg/kg/min for 24 h. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 6 hours (Peri vs Control) at 6 h; Group 1: mean 27.3 (SD 4.5); n=15, Group 2: mean 44 (SD 5); n=15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VAS at 24 hours (Peri vs Control) at 24 h; Group 1: mean 35.3 (SD 5.2); n=15, Group 2: mean 56 (SD 5); n=15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Cumulative requested doses of Morphine (mg) at 6 h (Peri vs Control) at 6 h; Group 1: mean 3 (SD 2.6); n=15, Group 2: mean 9 (SD 2.3); n=15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Cumulative requested doses of Morphine (mg) at 24 h (Peri vs Control) at 24 h; Group 1: mean 26.9 (SD 2.71); n=15, Group 2: mean 60 (SD 2.6); n=15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea+vomiting (Peri vs Control) at 24 h; Group 1: 1/15, Group 2: 8/15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Hadi 2013[367]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain VAS at 6 hours(Intra vs Control) at 6 h; Group 1: mean 36 (SD 5); n=15, Group 2: mean 44 (SD 5); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pain VAS at 24 hours (Intra vs Control) at 24 h; Group 1: mean 45.3 (SD 3.26); n=15, Group 2: mean 60 (SD 2.6); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: Cumulative requested doses of Morphine (mg) at 6 h (Intra vs Control) at 6 h; Group 1: mean 6.8 (SD 2.65); n=15, Group 2: mean 9 (SD 2.3); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Cumulative requested doses of Morphine (mg) at 24 h (Intra vs Control) at 24 h; Group 1: mean 45.3 (SD 3.26); n=15, Group 2: mean 60 (SD 2.6); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting (Intra vs Control) at 24 h; Group 1: 5/15, Group 2: 8/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Weinbroum 2003[1344]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=245)

Study	Weinbroum 2003[1344]
Countries and setting	Conducted in Israel; Setting: Post-anesthesia care unit
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients with ASA physical status I to III, scheduled for elective surgery from January to March 2002, were recruited for this randomized, double-blinded study. They gave written, informed consent approved by our human studies committee before undergoing abdominal general surgery, orthopedic surgery (knee replacement and disk surgery were excluded), or transthoracic lung biopsy or wedge resection under general anesthesia during the morning prime shift.
Exclusion criteria	Exclusion criteria included morbid obesity; disturbances of the central nervous system; chemical substance abuse; chronic pain; cardiovascular, hepatic, renal, or psychiatric diseases; age younger than 18 yr; and noncoherence. knee replacement and disk surgery were excluded
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Morphine+ketamine 53(20); Morphine 53(19). Gender (M:F): 132/113. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (abdominal general surgery, orthopedic surgery transthoracic lung biopsy orwedge resection under general anesthesia).
Indirectness of population	No indirectness
Interventions	(n=131) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Drug injections consisted of 15µg/kg of morphine plus 250 µg/kg of ketamine.. Duration postoperatively. Concurrent medication/care: General anesthesia was administered by the same team and consisted of IV sodium thiopental 2–3 mg/kg for induction, rocuronium infusion to facilitate tracheal intubation and obtain muscle relaxation, fentanyl 2–3 g/kg for intraoperative analgesia, and nitrous oxide/oxygen (2:1 L) enriched with isoflurane as deemed necessary by the attending anesthesi- ologist. All patients had volume-controlled ventilation. Neuromuscular relaxation was not reversed pharmacologically at the end of surgery: complete and normal recovery of neuromuscular activity was based on normal train-of-four and clinical criteria (ability to lift the head for 10 s, satisfactory hand-grasp strength, adequacy of respiratory rate, and normal ETco2) (2). No regional anesthesia was used in any of the patients.

Study	Weinbroum 2003[1344]
	While recovering in the postanesthesia care unit (PACU), all patients routinely received morphine IV (per patient request) consisting of 2-mg increments every 4–5 min until pain was relieved.. Indirectness: No indirectness (n=114) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Drug injections consisted of 30µg/kg of morphine plus saline. Patients were given up to three such IV boluses either until the pain VAS was =<4of10 or 10 min had passed. An anesthesiologist who did not participate in the study prepared the separate syringes. If pain was not attenuated with either regimen, a rescue dose of IM diclofenac 75 mg was given. Duration postoperatively. Concurrent medication/care: General anesthesia was administered by the same team and consisted of IV sodium thiopental 2–3 mg/kg for induction, rocuronium infusion to facilitate tracheal intubation and obtain muscle relaxation, fentanyl 2–3 g/kg for intraoperative analgesia, and nitrous oxide/oxygen (2:1 L) enriched with isoflurane as deemed necessary by the attending anesthesi-ologist. All patients had volume-controlled ventilation. Neuromuscular relaxation was not reversed pharmacologically at the end of surgery: complete and normal recovery of neuromuscular activity was based on normal train-of-four and clinical criteria (ability to lift the head for 10 s, satisfactory hand-grasp strength, adequacy of respiratory rate, and normal ETco2) (2). No regional anesthesia was used in any of the patients. While recovering in the postanesthesia care unit (PACU), all patients routinely received morphine IV (per patient request) consisting of 2-mg increments every 4–5 min until pain was relieved.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at postoperatively; 120 min after first morphine injection
Morphine+ketamine group ~ 1.5 Morphine+saline~4;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Diclofenac use (rescue medication) in PACU (number of patients) at postoperatively; Group 1: 5/131, Group 2: 17/114
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Diclofenac (rescue medication) use in ward (number of patients) at postoperatively; Group 1: 76/131, Group 2: 70/114
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Weinbroum 2003[1344]
Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: total morphine use(mg/kg) at postoperatively; no SD Morphine + ketamine group - 0.42; morphine group - 1.21; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: number of morphine injections at postoperatively; Group 1: mean 1.35 (SD 0.56); n=131, Group 2: mean 2.52 (SD 0.56); n=114 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: PONV in PACU at postoperatively; Group 1: 9/131, Group 2: 30/114 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: PONV in Ward at postoperatively; Group 1: 7/131, Group 2: 12/114 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Reeves 2001[1049]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=71)
Countries and setting	Conducted in Australia; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	all patients presenting for elective major abdominal surgery involving a midline incision were identified.
Exclusion criteria	not specified
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine group-54(13); control 47(14). Gender (M:F): 36/35. Ethnicity: NA
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2,3). 3. Type of surgery: lower and upper GI (major abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA morphine + ketamine 1mg/mL. Duration Intra+post op. Concurrent medication/care: The anesthetic technique was at the discretion of the anesthesiologist. Anesthesia consisted of IV induction with either thiopental or propofol, relaxation with cisatracurium or rucoronium and maintenance with sevoflurane or isoflurane in nitrous oxide. Intraoperative analgesia consisted of morphine plus or minus a dose of fentanyl at induction. . Indirectness: No indirectness (n=38) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA morphine 1 mg/mL. Duration intra+post op. Concurrent medication/care: The anesthetic technique was at the discretion of the

	anesthesiologist. Anesthesia consisted of IV induction with either thiopental or propofol, relaxation with cisatracurium or rucoronium and maintenance with sevoflurane or isoflurane in nitrous oxide. Intraoperative analgesia consisted of morphine plus or minus a dose of fentanyl at induction. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS (0 no pain 10 worst pain imaginable) at 6 hours at 6 h; Reported in the graph only
Ketamine group~2.5; control ~2.1;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3
- Actual outcome: Pain VRS (0 no pain 10 worst pain imaginable) at 12 hours at 12 h; Reported in the graph only
Ketamine group~1.8; control ~1.2;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: PCA use (mg/24h) at 24 h; Group 1: mean 77 mg/24 h (SD 31); n=36, Group 2: mean 71 mg/24 h (SD 38); n=35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea score (0-none, 2 severe) at 24 hours at 24 h; Median(10th to 90th percentile)
Ketamine group - 0 (0-1); control group 0 (0-1);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3
- Actual outcome: Nausea score (0-none, 2 severe) at 48 hours at 48 h; Median(10th to 90th percentile)
Ketamine group - 0 (0-1); control group 0 (0-2);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital

	readmission

Study	**Michelet 2007[719]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in France; Setting: Thoracic surgical unit of a University Teaching Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Eligible patients met the following criteria: age of 18 yr or older, planned lobectomy by posterolateral thoracotomy incision, and the choice of PCA in preference to other forms of postoperative analgesia.
Exclusion criteria	Exclusion criteria included the existence of a New York Heart Association class III–IV, a moderate to severe pre-existing chronic obstructive pulmonary disease (forced expira-tory volume in 1 s ,50% predicted),16 or a chronic renal in-sufficiency (creatinin clearance,80ml21 min21 1.73 m22).
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): morphine group 63 (42-76); ketamine group 64 (42-77). Gender (M:F): 36/14. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2,3). 3. Type of surgery: Not applicable (Lobectomy).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA device (APMw, AbbottLaboratories), containing morphine with ketamine 1 mg ml-1. All patients received i.v. acetaminophen 1 g every 6 h for 3 days. All additional analgesia such as i.v. ketoprofen and nefopam administered to patients during the following 3 days in order to lower the VAS to under 40 at mobilization were considered as rescue analgesia and recorded as such. The protocol for rescue analgesia consisted of the first administration of i.v. ketoprofen (first rescue analgesia line) 100 mg twice a day for 2 days. The second rescue analgesic line consisted of the possible adjunction of i.v. nefopam (100 mg first in a perfusion of 30

	min followed by continuous infusion of 400 mg per day for 2 days) in the case of residual pain with a VAS higher than 40.. Duration 3 days post op. Concurrent medication/care: All of them received the same premedication with oral hydroxyzine (1.5 mg kg21) 1h before surgery. Anaesthetic management was standardized for all study patients. Induction of anaesthesia was performed with propofol (2 mg kg21), sufentanil (0.3 mg kg21), and cisatracurium (0.15 mg kg21). Anaesthesia was maintained with sevoflurane, sufentanil, and cisatracurium titrated according to the patients' needs. Additional analgesia, such as non-steroidal anti-inflammatory drugs, regional or local anaesthetic techniques were not allowed during the operative period . Indirectness: No indirectness (n=25) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA device (APMw, AbbottLaboratories), containing morphine 1 mg ml-1(Group M). All patients received i.v. acetaminophen 1 g every 6 h for 3 days. All additional analgesia such as i.v. ketoprofene and nefopam administered to patients during the following 3 days in order to lower the VAS to under 40 at mobilization were considered as rescue analgesia and recorded as such. The protocol for rescue analgesia consisted of the first administration of i.v. ketoprofen (first rescue analgesia line) 100 mg twice a day for 2 days. The second rescue analgesic line consisted of the possible adjunction of i.v. nefopam (100 mg first in a perfusion of 30 min followed by continuous infusion of 400 mg per day for 2 days) in the case of residual pain with a VAS higher than 40.. Duration 3 days post op. Concurrent medication/care: All of them received the same premedication with oral hydroxyzine (1.5 mg kg21) 1h before surgery. Anaesthetic management was standardized for all study patients. Induction of anaesthesia was performed with propofol (2 mg kg21), sufentanil (0.3 mg kg21), and cisatracurium (0.15 mg kg21). Anaesthesia was maintained with sevoflurane, sufentanil, and cisatracurium titrated according to the patients' needs. Additional analgesia, such as non-steroidal anti-inflammatory drugs, regional or local anaesthetic techniques were not allowed during the operative period . Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO	

Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain VAS at post op 24 hours; Group 1: mean 30 (SD 14); n=24, Group 2: mean 40 (SD 20); n=24 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Cumulative morphine consumption at post op 24 hours; Reported in the graph only Ketamine~25; Control~30; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 - Actual outcome: Need for rescue medication at post op; Group 1: 11/24, Group 2: 16/24 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting at post op; Group 1: 6/24, Group 2: 7/24 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Tang 2010[1240]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in China; Setting: outpatient
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a

Inclusion criteria	80 women ASA 1 and 2 undergoing outpatient laparoscopic procedures in west china second hospital were included in the study.
Exclusion criteria	morbid obesity, clinically significant cardiovascular, respiratory or hepatic disease; allergy to anesthetics, or history of drug or alcohol abuse. patients currently taking sedative or analgesic drugs were also excluded.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Fentanyl+ketamine - 31.2(4); fentanyl 31(3.5). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (Gynecologic diagnostic laparoscopy).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. after 150 seconds, 10 mg/mL. immediately propofol, 2 mg mL was administered in all patients at 4 mg/s. Duration post op. Concurrent medication/care: sedation was initiated with fentanyl 1µg/kg, administered intravenously over 10 seconds. . Indirectness: No indirectness (n=40) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. after 150 seconds, 0.05mL/kg of 9 % normal saline. immediately propofol, 2 mg mL was administered in all patients at 4 mg/s. Duration post op. Concurrent medication/care: sedation was initiated with fentanyl 1µg/kg, administered intravenously over 10 seconds. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain VAS at 24 hours at 24 hours; median
ketamine group 70(69-75); control 72(66-80);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: rescue Propofol (number of people) at post op; Group 1: 7/40, Group 2: 32/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: rescue Propofol (mean dose) at post op; Group 1: mean 0.4 (SD 0.5); n=40, Group 2: mean 1.6 (SD 0.6); n=40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting+Respiratory depresion at post op; Group 1: 10/40, Group 2: 20/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Length of stay in intensive care unit - Actual outcome: time to discharge (From PACU) minutes at post op; Group 1: mean 103.1 minutes (SD 19.3); n=40, Group 2: mean 97.4 minutes (SD 18.2); n=40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of hospital stay ; Hospital readmission

Study	**Unlugenc 2002[1287]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in Turkey; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	66 ASA Physical status 1 or 2 patients, between the ages of 18 and 59 years, scheduled for elective major abdominal surgery with general anaesthesia were recruited.
Exclusion criteria	Inability to use PCA, long term use of opioid medications, and history of chronic pain
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Tramadol-ketamine - 48(4); Tramadol - 47(2). Gender (M:F): 26/17. Ethnicity: not stated

Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (Major abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA Tramadol 5mg/ml + ketamine 1 mg/ml. In all groups 4 mg odansetron and and 0.4 mg/kg meperidine were prescribed intravenously every 4 hours as rescue antiemetic and analgesic respectively. Duration post op. Concurrent medication/care: All patients were premedicated with intravenous midazolam 0.1 mg/kg 60 min before operation. anesthesia was induced with thiopenthal sodium (5mg/kg) and maintained with 1.5-2 % sevoflurane in a mixture of 66% nitrous oxide and 34 % oxygen. Indirectness: No indirectness (n=21) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA Tramadol 5 mg/ml. In all groups 4 mg odansetron and and 0.4 mg/kg meperidine were prescribed intravenously every 4 hours as rescue antiemetic and analgesic respectively. Duration post op. Concurrent medication/care: All patients were premedicated with intravenous midazolam 0.1 mg/kg 60 min before operation. anesthesia was induced with thiopenthal sodium (5mg/kg) and maintained with 1.5-2 % sevoflurane in a mixture of 66% nitrous oxide and 34 % oxygen. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS at 6 hours at 6 hours; Median (range)
tramadol+ketamine - 2(1-3); tramadol 2 (1-3);
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VRS at 24hours at 24 hours; Median (range)
tramadol+ketamine - 1(1-2); tramadol 1 (1-2);
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Mean Bolus PCA Tramadol doses (mg) 6 hours at 6 hours; Group 1: mean 55 mg (SD 43); n=22, Group 2: mean 120 mg (SD 47); n=21
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Mean Bolus PCA Tramadol doses (mg) 24 hours at 24 hours; Group 1: mean 70 mg (SD 89); n=22, Group 2: mean 180 mg (SD 32); n=21

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: total PCA Tramadol doses (mg) 6 hours at 6 hours; Group 1: mean 280 mg (SD 44); n=22, Group 2: mean 405 mg (SD 51); n=21 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: total PCA Tramadol doses (mg) 24 hours at 24 hours; Group 1: mean 850 mg (SD 56); n=22, Group 2: mean 975 mg (SD 31); n=21 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea at 24 hours; Group 1: 6/22, Group 2: 9/21 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Yalcin 2012[1382]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Turkey; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	enrolled 90 patients of ASA physical status I-II scheduled for elective total abdominal hysterectomy
Exclusion criteria	Patients with a history of psychiatric disorders, chronic pain, renal, cardiac orhematological insufficiency, chronic analgesic or opioid treatment, age dbelow 35 yr and above 70 yr, inability to use a patient-controlled analgesia(PCA) device and duration of surgery over 120 min were excluded from the study
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine group - 48.26(5.66); control group 48.14(5.98). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (Hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients in Ketamine group received intravenous (iv) bolus ketamine 0.5 mg/kg, before the induction of anesthesia. The patients in ketamine group also received a maintenance infusion of5 µg/kg/min ketamine intraoperatively until skin closure. When VAS score was less than 5, patients were connected to a PCA device set to deliver 1mg morphine as an iv bolus with a 6-min lockout interval; continuous infusionwas not allowed. This PCA regimen was continued for 48 hrs. Duration intra+48 h post op. Concurrent medication/care: All patients were premedicated with 10 mg oral diazepam the night before surgery and 10 mg intramuscular diazepam one hour before surgery.General anesthesia was induced with remifentanil 1 µg/kg and propofol 1.5-2 mg /kg followed by atracurium 0.5mg/kg to facilitate tracheal intubation. Anesthesia was maintained with 0.4

	µg/kg/minremifentanil infusion and desflurane 0.5 MAC.. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients in controlgroup received physiologic saline; beforethe induction of anesthesia. When VAS score was less than 5, patients wereconnected to a PCA device set to deliver 1 mg morphine as an iv bolus with a6-min lockout interval; continuous infusion was not allowed. This PCA regimenwas continued for 48 hrs. Duration intra+48 h post op. Concurrent medication/care: All patients were premedicated with 10 mg oral diazepam the night before surgery and 10 mg intramuscular diazepam one hour before surgery.General anesthesia was induced with remifentanil 1 µg/kg and propofol 1.5-2 mg /kg followed by atracurium 0.5mg/kg to facilitate tracheal intubation. Anesthesia was maintained with 0.4 µg/kg/minremifentanil infusion and desflurane 0.5 MAC.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain VAS at 6 hours post op at 6 hours post op; reported in the graph ketamine~2; control~2.5; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3 - Actual outcome: Pain VAS at 24 hours post op at 24 hours post op; reported in the graph ketamine~0; control~0.25; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: morphine (PCA) consumption 6 hours post op at 6 hours post op; Group 1: mean 23.53 (SD 8.96); n=26, Group 2: mean 36.7 (SD 7.16); n=27 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3 - Actual outcome: morphine (PCA) consumption 24 hours post op at 24 hours post op; Group 1: mean 35.34 (SD 13.71); n=26, Group 2: mean 73.03 (SD 22.41); n=27 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3	
Protocol outcomes not reported by the	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ;

study	Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Snijdelaar 2004[1176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Canada; Setting: department of anesthesia
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Inclusion criteria were ability to speak dutch, 17 18 years of age, ASA class1-3, stable or no significant central nervous system, respiratory cardiac, hepatic, renal or endocrine dysfunction and/or endocrine dysfunction and/or any significant sequelae. body weight 60-100 kg with a body mass index =< 30kgm-²
Exclusion criteria	history significant psychopathology, chronic pain or chronic use of opioid analgesics, previous allergies or adverse reactions to opiod analgesics, ingestion of antitussive medication (dextromethorphan) within 48 hours of surgery, history of alcohol or drug dependency or abuse.
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): Ketamine/morphine. Gender (M:F): all male. Ethnicity: not stated
Further population details	1. Age: Not stated / Unclear 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1-3). 3. Type of surgery: urology (prostatectomy).
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. The PCA system was programmed to deliver a bolus of 0.5 ml, corresponding to a bolus dose of 0.5 mg s(+)-ketamine plus 1 mg of morphine for the ketamine／morphine group . Duration post op. Concurrent medication/care: Premedication consisted of oral midazolam 7.5 mg(administered 45–60 min before the expectedtime of induction of general anaesthesia). An additional 2 mg midazolam was given intravenously after insertion of a venousline. Five minutes before induction with propofol(2 mg.kg)1) and fentanyl (2 lg.kg)1), patients received a bolus injection of 0.1 ml.kg)1 s(+)-ketamine (ketamine⁄morphine group) or saline (saline／morphine group),followed by a continuous infusion of 0.002 ml.kg)1.min)1of the same agent. For patients in the ketamine／morphine group,this amounted to a bolus dose of 100 lg.kg)1 s(+)-ketamine and a continuous infusion of 2 lg.kg)1.min)1s(+)-ketamine. After induction,

	0.6 mg.kg)1 rocuroniumwas given to facilitate tracheal intubation. Anaesthesia was maintained with isoflurane inN2O/O2 (60%/40%) aiming at an end expiratory concentration of isoflurane of 0.7%.Further rocuronium 0.1–0.2 mg.kg)1 was given when necessary. Morphine in a dose of 50 lg.kg)1 was given when there were signs of inadequate analgesia (increase in blood pressure or heart rate above 10% of baseline value). The continuous infusion of s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group) was stopped at skin closure. At the conclusion of surgery,neuromuscular blockade was reversed (when necessary) with neostigmine (0.05 mg.kg)1) and atropine (0.01–0.02 mg.kg)1). . Indirectness: No indirectness (n=14) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. The PCA system was programmed to deliver a bolus of 0.5 ml, corresponding to 1 mg morphine for the saline/morphine group.. Duration post op. Concurrent medication/care: Premedication consisted of oral midazolam 7.5 mg(administered 45–60 min before the expectedtime of induction of general anaesthesia). An additional 2 mg midazolam was given intravenously after insertion of a venousline. Five minutes before induction with propofol(2 mg.kg)1) and fentanyl (2 lg.kg)1), patients received a bolus injection of 0.1 ml.kg)1 s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group),followed by a continuous infusion of 0.002 ml.kg)1.min)1of the same agent. For patients in the ketamine/morphine group,this amounted to a bolus dose of 100 lg.kg)1 s(+)-ketamine and a continuous infusion of 2 lg.kg)1.min)1s(+)-ketamine. After induction, 0.6 mg.kg)1 rocuroniumwas given to facilitate tracheal intubation. Anaesthesia was maintained with isoflurane inN2O/O2 (60%/40%) aiming at an end expiratory

	concentration of isoflurane of 0.7%.Further rocuronium 0.1–0.2 mg.kg)1 was given when necessary. Morphine in a dose of 50 lg.kg)1 was given when there were signs of inadequate analgesia (increase in blood pressure or heart rate above 10% of baseline value). The continuous infusion of s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group) was stopped at skin closure. At the conclusion of surgery,neuromuscular blockade was reversed (when necessary) with neostigmine (0.05 mg.kg)1) and atropine (0.01–0.02 mg.kg)1). . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 4 hours at 4 hours post op; Group 1: mean 1.4 (SD 1.2); n=13, Group 2: mean 2.9 (SD 1.6); n=12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2
- Actual outcome: Pain VAS at 24 hours at 24 hours post op; Group 1: mean 1.2 (SD 1); n=13, Group 2: mean 2 (SD 1.4); n=12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: cumulative post op PCA morphine consumption at post op; Group 1: mean 47.9 (SD 26.2); n=13, Group 2: mean 73.4 (SD 34.8); n=12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: nausea 24 h post op at 24 h post op; Group 1: mean 1.1 (SD 2.1); n=13, Group 2: mean 0.4 (SD 0.6); n=12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2
- Actual outcome: nausea 48 h post op at 48 h post op; Group 1: mean 0.1 (SD 0.4); n=13, Group 2: mean 0.4 (SD 1); n=12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2
- Actual outcome: vomiting 24 h post op at 24 h post op; Group 1: 0/13, Group 2: 1/11
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2
- Actual outcome: vomiting 48 h post op at 48 h post op; Group 1: 0/13, Group 2: 1/11

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Hadi 2013[367]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Hungary; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Inclusion criterion was that the patient was adult who had a level of education which enabled him to understand the use of the patient-controlled analgesia technique. Those patients who had used bed rest and had physical therapy sessions by licensed physical therapists to relieve their lower back pain at least 48 h prior to surgery were included in the trial.
Exclusion criteria	Exclusion criteria were that patients with severe back pain who were receiving chronic narcotic analgesic treatment were excluded, as were patients with major systemic diseases.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Periop 55(2.6); intra 69(2.6); CTRL 71(2.6). Gender (M:F): 21/24. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (microdiscectomy surgery).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Peri group - ketamine (1 µg/kg/min) both intra- and postoperatively. Duration 24 hours. Concurrent medication/care: All patients were given midazolam 0.25 mg/kg orally, 30 min before surgery as a premedication. On arrival at the operating theater, the following drugs were given: propofol 2 mg/kg as an IV bolus for induction in all the three groups followed by atracurium 0.6 mg/kg to facilitate orotracheal intubation. Sevoflurane (1–1.5% v/v) in a carrier gas mixture of 1:1 nitorus oxide/oxygen was used for all patients. Anesthesia was pre-induced using

	remifentanil 1 lg/kg for the three groups followed by a remifentanil infusion at a dose of 0.2 lg/kg/min. A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 lg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 lg/kg/min administered using two different cannulas. All drugs were stopped at the end of the operation except for G3 where the ketamine was continued to be administered at 1 lg/kg/min for 24 h . Indirectness: No indirectness (n=15) Intervention 2: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Intra group - ketamine(1 µg/kg/min) intra-operatively. Duration 24 hours. Concurrent medication/care: All patients were given midazolam 0.25 mg/kg orally, 30 min before surgery as a premedication. On arrival at the operating theater, the following drugs were given: propofol 2 mg/kg as an IV bolus for induction in all the three groups followed by atracurium 0.6 mg/kg to facilitate orotracheal intubation. Sevoflurane (1–1.5% v/v) in a carrier gas mixture of 1:1 nitorus oxide/oxygen was used for all patients. Anesthesia was pre-induced using remifentanil 1 lg/kg for the three groups followed by a remifentanil infusion at a dose of 0.2 lg/kg/min. A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 lg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 lg/kg/min administered using two different cannulas. All drugs were stopped at the end of the operation except for G3 where the ketamine was continued to be administered at 1 lg/kg/min for 24 h. Indirectness: No indirectness (n=15) Intervention 3: Opioid (IV) and placebo - Opioid + placebo. Control group - received normal saline, A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 µg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 µg/kg/min administered using two different cannulas.

	. Duration 24 hours. Concurrent medication/care: All patients were given midazolam 0.25 mg/kg orally, 30 min before surgery as a premedication. On arrival at the operating theater, the following drugs were given: propofol 2 mg/kg as an IV bolus for induction in all the three groups followed by atracurium 0.6 mg/kg to facilitate orotracheal intubation. Sevoflurane (1–1.5% v/v) in a carrier gas mixture of 1:1 nitorus oxide/oxygen was used for all patients. Anesthesia was pre-induced using remifentanil 1 lg/kg for the three groups followed by a remifentanil infusion at a dose of 0.2 lg/kg/min. A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 lg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 lg/kg/min administered using two different cannulas. All drugs were stopped at the end of the operation except for G3 where the ketamine was continued to be administered at 1 lg/kg/min for 24 h. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 6 hours (Peri vs Control) at 6 h; Group 1: mean 27.3 (SD 4.5); n=15, Group 2: mean 44 (SD 5); n=15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VAS at 24 hours (Peri vs Control) at 24 h; Group 1: mean 35.3 (SD 5.2); n=15, Group 2: mean 56 (SD 5); n=15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Cumulative requested doses of Morphine (mg) at 6 h (Peri vs Control) at 6 h; Group 1: mean 3 (SD 2.6); n=15, Group 2: mean 9 (SD 2.3); n=15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Cumulative requested doses of Morphine (mg) at 24 h (Peri vs Control) at 24 h; Group 1: mean 26.9 (SD 2.71); n=15, Group 2: mean 60 (SD 2.6); n=15
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

	Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting (Peri vs Control) at 24 h; Group 1: 1/15, Group 2: 8/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain VAS at 6 hours(Intra vs Control) at 6 h; Group 1: mean 36 (SD 5); n=15, Group 2: mean 44 (SD 5); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pain VAS at 24 hours (Intra vs Control) at 24 h; Group 1: mean 45.3 (SD 3.26); n=15, Group 2: mean 60 (SD 2.6); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: Cumulative requested doses of Morphine (mg) at 6 h (Intra vs Control) at 6 h; Group 1: mean 6.8 (SD 2.65); n=15, Group 2: mean 9 (SD 2.3); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Cumulative requested doses of Morphine (mg) at 24 h (Intra vs Control) at 24 h; Group 1: mean 45.3 (SD 3.26); n=15, Group 2: mean 60 (SD 2.6); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting (Intra vs Control) at 24 h; Group 1: 5/15, Group 2: 8/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Weinbroum 2003[1344]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=245)
Countries and setting	Conducted in Israel; Setting: Post-anesthesia care unit
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients with ASA physical status I to III, scheduled for elective surgery from January to March 2002, were recruited for this randomized, double-blinded study. They gave written, informed consent approved by our human studies committee before undergoing abdominal general surgery, orthopedic surgery (knee replacement and disk surgery were excluded), or transthoracic lung biopsy or wedge resection under general anesthesia during the morning prime shift.
Exclusion criteria	Exclusion criteria included morbid obesity; disturbances of the central nervous system; chemical substance abuse; chronic pain; cardiovascular, hepatic, renal, or psychiatric diseases; age younger than 18 yr; and noncoherence. knee replacement and disk surgery were excluded
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Morphine+ketamine 53(20); Morphine 53(19). Gender (M:F): 132/113. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (abdominal general surgery, orthopedic surgery transthoracic lung biopsy orwedge resection under general anesthesia).
Indirectness of population	No indirectness
Interventions	(n=131) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Drug injections consisted of 15µg/kg of morphine plus 250 µg/kg of ketamine.. Duration postoperatively. Concurrent medication/care: General anesthesia was administered by the same team and consisted of IV sodium thiopental 2–3 mg/kg for induction, rocuronium infusion to facilitate tracheal intubation and obtain muscle relaxation, fentanyl 2–3 g/kg for intraoperative analgesia, and nitrous oxide/oxygen (2:1 L) enriched with isoflurane as deemed necessary by the attending anesthesi- ologist. All patients had volume-controlled ventilation. Neuromuscular relaxation was not reversed

	pharmacologically at the end of surgery: complete and normal recovery of neuromuscular activity was based on normal train-of-four and clinical criteria (ability to lift the head for 10 s, satisfactory hand-grasp strength, adequacy of respiratory rate, and normal ETco2) (2). No regional anesthesia was used in any of the patients. While recovering in the postanesthesia care unit (PACU), all patients routinely received morphine IV (per patient request) consisting of 2-mg increments every 4–5 min until pain was relieved.. Indirectness: No indirectness (n=114) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Drug injections consisted of 30µg/kg of morphine plus saline. Patients were given up to three such IV boluses either until the pain VAS was =<4of10 or 10 min had passed. An anesthesiologist who did not participate in the study prepared the separate syringes. If pain was not attenuated with either regimen, a rescue dose of IM diclofenac 75 mg was given. Duration postoperatively. Concurrent medication/care: General anesthesia was administered by the same team and consisted of IV sodium thiopental 2–3 mg/kg for induction, rocuronium infusion to facilitate tracheal intubation and obtain muscle relaxation, fentanyl 2–3 g/kg for intraoperative analgesia, and nitrous oxide/oxygen (2:1 L) enriched with isoflurane as deemed necessary by the attending anesthesi-ologist. All patients had volume-controlled ventilation. Neuromuscular relaxation was not reversed pharmacologically at the end of surgery: complete and normal recovery of neuromuscular activity was based on normal train-of-four and clinical criteria (ability to lift the head for 10 s, satisfactory hand-grasp strength, adequacy of respiratory rate, and normal ETco2) (2). No regional anesthesia was used in any of the patients. While recovering in the postanesthesia care unit (PACU), all patients routinely received morphine IV (per patient request) consisting of 2-mg increments every 4–5 min until pain was relieved.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at postoperatively; 120 min after first morphine injection
Morphine+ketamine group ~ 1.5 Morphine+saline~4;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Diclofenac use (rescue medication) in PACU (number of patients) at postoperatively; Group 1: 5/131, Group 2: 17/114
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Diclofenac (rescue medication) use in ward (number of patients) at postoperatively; Group 1: 76/131, Group 2: 70/114 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: total morphine use(mg/kg) at postoperatively; no SD Morphine + ketamine group - 0.42; morphine group - 1.21; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: number of morphine injections at postoperatively; Group 1: mean 1.35 (SD 0.56); n=131, Group 2: mean 2.52 (SD 0.56); n=114 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: PONV in PACU at postoperatively; Group 1: 9/131, Group 2: 30/114 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: PONV in Ward at postoperatively; Group 1: 7/131, Group 2: 12/114 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Reeves 2001[1049]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=71)
Countries and setting	Conducted in Australia; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	all patients presenting for elective major abdominal surgery involving a midline incision were identified.
Exclusion criteria	not specified
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine group-54(13); control 47(14). Gender (M:F): 36/35. Ethnicity:
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2,3). 3. Type of surgery: lower and upper GI (major abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA morphine + ketamine 1mg/mL. Duration Intra+post op. Concurrent medication/care: The anesthetic technique was at the discretion of the anesthesiologist. Anesthesia consisted of IV induction with either thiopental or propofol, relaxation with cisatracurium or rucoronium and maintenance with sevoflurane or isoflurane in nitrous oxide. Intraoperative analgesia consisted of morphine plus or minus a dose of fentanyl at induction. . Indirectness: No indirectness (n=38) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA morphine 1 mg/mL. Duration intra+post op. Concurrent medication/care: The anesthetic technique was at the discretion of the

	anesthesiologist. Anesthesia consisted of IV induction with either thiopental or propofol, relaxation with cisatracurium or rucoronium and maintenance with sevoflurane or isoflurane in nitrous oxide. Intraoperative analgesia consisted of morphine plus or minus a dose of fentanyl at induction. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS (0 no pain 10 worst pain imaginable) at 6 hours at 6 h; Reported in the graph only
Ketamine group~2.5; control ~2.1;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3
- Actual outcome: Pain VRS (0 no pain 10 worst pain imaginable) at 12 hours at 12 h; Reported in the graph only
Ketamine group~1.8; control ~1.2;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: PCA use (mg/24h) at 24 h; Group 1: mean 77 mg/24 h (SD 31); n=36, Group 2: mean 71 mg/24 h (SD 38); n=35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea score (0-none, 2 severe) at 24 hours at 24 h; Median(10th to 90th percentile)
Ketamine group - 0 (0-1); control group 0 (0-1);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3
- Actual outcome: Nausea score (0-none, 2 severe) at 48 hours at 48 h; Median(10th to 90th percentile)
Ketamine group - 0 (0-1); control group 0 (0-2);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital

readmission

Study	Michelet 2007[719]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in France; Setting: Thoracic surgical unit of a University Teaching Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Eligible patients met the following criteria: age of 18 yr or older, planned lobectomy by posterolateral thoracotomy incision, and the choice of PCA in preference to other forms of postoperative analgesia.
Exclusion criteria	Exclusion criteria included the existence of a New York Heart Association class III–IV, a moderate to severe pre-existing chronic obstructive pulmonary disease (forced expiratory volume in 1 s ,50% predicted),16 or a chronic renal insufficiency (creatinin clearance,80ml21 min21 1.73 m22).
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): morphine group 63 (42-76); ketamine group 64 (42-77). Gender (M:F): 36/14. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2,3). 3. Type of surgery: Not applicable (Lobectomy).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA device (APMw, AbbottLaboratories), containing morphine with ketamine 1 mg ml-1. All patients received i.v. acetaminophen 1 g every 6 h for 3 days. All additional analgesia such as i.v. ketoprofen and nefopam administered to patients during the following 3 days in order to lower the VAS to under 40 at mobilization were considered as rescue analgesia and recorded as such. The protocol for rescue analgesia consisted of the first administration of i.v. ketoprofen (first rescue analgesia line) 100 mg twice a day for 2 days. The second rescue analgesic line consisted of the possible adjunction of i.v. nefopam (100 mg first in a perfusion of 30 min followed by continuous infusion of 400 mg per day for 2 days) in the case of residual pain with a VAS higher than 40.. Duration 3 days post op. Concurrent medication/care: All of them received the same premedication with oral hydroxyzine (1.5 mg kg21) 1h before surgery. Anaesthetic management was

	standardized for all study patients. Induction of anaesthesia was performed with propofol (2 mg kg21), sufentanil (0.3 mg kg21), and cisatracurium (0.15 mg kg21). Anaesthesia was maintained with sevoflurane, sufentanil, and cisatracurium titrated according to the patients' needs. Additional analgesia, such as non-steroidal anti-inflammatory drugs, regional or local anaesthetic techniques were not allowed during the operative period . Indirectness: No indirectness (n=25) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA device (APMw, AbbottLaboratories), containing morphine 1 mg ml-1(Group M). All patients received i.v. acetaminophen 1 g every 6 h for 3 days. All additional analgesia such as i.v. ketoprofene and nefopam administered to patients during the following 3 days in order to lower the VAS to under 40 at mobilization were considered as rescue analgesia and recorded as such. The protocol for rescue analgesia consisted of the first administration of i.v. ketoprofen (first rescue analgesia line) 100 mg twice a day for 2 days. The second rescue analgesic line consisted of the possible adjunction of i.v. nefopam (100 mg first in a perfusion of 30 min followed by continuous infusion of 400 mg per day for 2 days) in the case of residual pain with a VAS higher than 40.. Duration 3 days post op. Concurrent medication/care: All of them received the same premedication with oral hydroxyzine (1.5 mg kg21) 1h before surgery. Anaesthetic management was standardized for all study patients. Induction of anaesthesia was performed with propofol (2 mg kg21), sufentanil (0.3 mg kg21), and cisatracurium (0.15 mg kg21). Anaesthesia was maintained with sevoflurane, sufentanil, and cisatracurium titrated according to the patients' needs. Additional analgesia, such as non-steroidal anti-inflammatory drugs, regional or local anaesthetic techniques were not allowed during the operative period . Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain VAS at post op 24 hours; Group 1: mean 30 (SD 14); n=24, Group 2: mean 40 (SD 20); n=24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Cumulative morphine consumption at post op 24 hours; Reported in the graph only Ketamine~25; Control~30; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 - Actual outcome: Need for rescue medication at post op; Group 1: 11/24, Group 2: 16/24 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting at post op; Group 1: 6/24, Group 2: 7/24 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Tang 2010[1240]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in China; Setting: outpatient
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	80 women ASA 1 and 2 undergoing outpatient laparoscopic procedures in west china second hospital were included in the study.
Exclusion criteria	morbid obesity, clinically significant cardiovascular, respiratory or hepatic disease; allergy to anesthetics, or history of drug or alcohol abuse. patients currently taking sedative or analgesic drugs were also excluded.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Fentanyl+ketamine - 31.2(4); fentanyl 31(3.5). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (Gynecologic diagnostic laparoscopy).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. after 150 seconds, 10 mg/mL. immediately propofol, 2 mg mL was administered in all patients at 4 mg/s. Duration post op. Concurrent medication/care: sedation was initiated with fentanyl 1µg/kg, administered intravenously over 10 seconds. . Indirectness: No indirectness (n=40) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. after 150 seconds, 0.05mL/kg of 9 % normal saline. immediately propofol, 2 mg mL was administered in all patients at 4 mg/s. Duration post op. Concurrent medication/care: sedation was initiated with fentanyl 1µg/kg, administered intravenously over 10 seconds. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO	

Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain VAS at 24 hours at 24 hours; median ketamine group 70(69-75); control 72(66-80); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: rescue Propofol (number of people) at post op; Group 1: 7/40, Group 2: 32/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: rescue Propofol (mean dose) at post op; Group 1: mean 0.4 (SD 0.5); n=40, Group 2: mean 1.6 (SD 0.6); n=40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting+Respiratory depresion at post op; Group 1: 10/40, Group 2: 20/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Length of stay in intensive care unit - Actual outcome: time to discharge (From PACU) minutes at post op; Group 1: mean 103.1 minutes (SD 19.3); n=40, Group 2: mean 97.4 minutes (SD 18.2); n=40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of hospital stay ; Hospital readmission

Study	Dullenkopf 2009[255]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Switzerland; Setting:
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Inclusion criteria were: general anaesthesia for general surgical or orthopaedic operations anticipated to last 30 to 120 minutes, assumed hospital stay of 48 hours and age 18 years or older.
Exclusion criteria	Exclusion criteria included contraindications to IV ketamine (e.g. insufficiently or untreated elevated arterial blood pressure, patients in whom an increase of arterial blood pressure would be potentially dangerous, patients with a history of previous stroke or intracerebral bleeding, arterial aneurysm, insufficiently treated hyperthyroidism, hypersensitivity to ketamine or itspreservative benzethonium chloride), an ASA physical status greater than III, inability to communicate appropriately, pregnancy, severe renal and hepatic dysfunction, known allergies to any other study medications, contraindications to maintenance of general anaesthesia using propofol, actual therapy with psychoactive drugs or opiates, history of severe psychological disturbances, planned postoperative admission to the intensive care unit and patients weighing more than 120 kg.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine - 52.65 (18.1); control - 52.3 (17.9). Gender (M:F): 45/65. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 3. Type of surgery: ortho/large joint replacement (orthopaedic).
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine 0.15 mg/kg or 0.5mg/kg

	In the PACU,patients received analgesia with nurse-controlled morphine IV (in doses of 0.03 mg/kg) if they had a VAS ≥3. Additionally, paracetamol 1 g IV could be administered. On the ward, all patients were given novaminsulfone 1 g IV up to four times per day, if necessary. The next step was paracetamol 1 g orally up to four times a day. Morphine 0.03 mg/kg IV was used as rescue medication. Rescue medication for postoperative nausea or vomiting consisted of ondansetron 4 mg IV up to twice daily. . Duration intra+post op. Concurrent medication/care: For premedication, 7.5 mg midazolam was administered to all patients orally 45 minutes before induction of anaesthesia. On arrival in the operating unit, electrocardiogram, blood pressure and pulse oximetry monitoring were commenced. Induction of general anaesthesia was achieved with propofol 1.5 to 2.5 mg/kg IV and fentanyl 1.5 µg/kg IV. If tracheal intubation was deemed necessary, muscle relaxation was achieved by atracurium 0.5 to 0.6 mg/kg of IV. Anaesthesia was maintained with propofol, plus nitrous oxide in oxygen, supplemented by up to one additional fentanyl dose if required for intraoperative analgesia (0.75 to 1.5 µg/kg), and remifentanil infusion, dosed according to the attending anaesthetist. Fifteen minutes before the end of surgery, all patients were given novaminsulfone (a non-steroidal anti-inflammatory drug) 1 g IV. If there was a history of postoperative nausea or vomiting, ondansetron 4 mg IV was administered intraoperatively.. Indirectness: No indirectness (n=33) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. normal saline In the PACU,patients received analgesia with nurse-controlled morphine IV (in doses of 0.03 mg/kg) if they had a VAS ≥3. Additionally, paracetamol 1 g IV could be administered. On the ward, all patients were given novaminsulfone 1 g IV up to four times per day, if necessary. The next step was paracetamol 1 g orally up to four times a day. Morphine 0.03 mg/kg IV was used as rescue medication. Rescue medication for postoperative nausea or vomiting consisted of ondansetron 4 mg IV up to twice daily. . Duration intra+post op. Concurrent medication/care: For premedication, 7.5 mg midazolam was administered to all patients orally 45 minutes before induction of anaesthesia. On arrival in the operating unit, electrocardiogram, blood pressure and pulse oximetry monitoring were commenced. Induction of

	general anaesthesia was achieved with propofol 1.5 to 2.5 mg/kg IV and fentanyl 1.5 µg/kg IV. If tracheal intubation was deemed necessary, muscle relaxation was achieved by atracurium 0.5 to 0.6 mg/kg of IV. Anaesthesia was maintained with propofol, plus nitrous oxide in oxygen, supplemented by up to one additional fentanyl dose if required for intraoperative analgesia (0.75 to 1.5 µg/kg), and remifentanil infusion, dosed according to the attending anaesthetist. Fifteen minutes before the end of surgery, all patients were given novaminsulfone (a non-steroidal anti-inflammatory drug) 1 g IV. If there was a history of postoperative nausea or vomiting, ondansetron 4 mg IV was administered intraoperatively.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score arriving in PACU at post op; Median (range)
Ketamine(0.15mg/kg) 3(0-10); ketamine(0.5mg/kg) 4(0-9); Control group 4 (0-9)
;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Morphine consumption in PACU at post op; Group 1: mean 7.879 mg (SD 7.13); n=77, Group 2: mean 8.3 mg (SD 6.8); n=33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Cumulative morphine consumption in 24 hours at 24 hours; Group 1: mean 8.766 mg (SD 9.035); n=77, Group 2: mean 10.3 mg (SD 6.8); n=33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Length of stay in intensive care unit
- Actual outcome: Length of stay in PACU (minutes) post op at post op; Group 1: mean 122.2 (SD 44.03); n=77, Group 2: mean 108.9 (SD 29.1); n=33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ;

Length of hospital stay ; Hospital readmission

Study	Lak 2010[566]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Iran; Setting: general hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Sixty subjects who were candidate for nephrectomy as donors were selected in Baqiyatallah Hospital. All subjects were donors of renal transplantation admitted to the hospital from May 2007 to December 2008. During the day before surgery, an anesthesiologist visited the patients and included the ones with the American Society of Anesthesiologists (ASA) class I criteria.
Exclusion criteria	Define
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): ketamine group 27.3 (5.5); Placebo 27.9 (3.9). Gender (M:F): 44/6. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 3. Type of surgery: urology (nephrectomy).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. In the ketamine group, ketamine was administered separately with an initial bolus of 0.5 mg/kg followed by infusion of 2 µg/kg/min during the first 24 hours and 1 µg/kg/min in the following 24 hours. In both groups, if the patients requested analgesia, 2 mg of morphine was administered by nurses without any limitations as the loading dose followed by 1 mg every 5 minutes until the VAS became less than 4.. Duration 48 hours. Concurrent medication/care: All patients had the same anesthesia protocol. They received 0.1 mg/kg of morphine as premedication. Anesthesia was induced by thiopental (5-7mg/kg) and atracurium (0.5 mg/kg) afterwards. Maintenance of anesthesia was done with isoflurane (proportionate to the patients' hemodynamic status), N2O (50%) and O2 (50%).. Indirectness: No indirectness (n=25) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. In the placebo group, ketamine was replaced by saline serum as placebo and administered under the same conditions. In both groups, if the patients requested analgesia, 2 mg of morphine was administered by nurses without

	any limitations as the loading dose followed by 1 mg every 5 minutes until the VAS became less than 4.. Duration 48 hours. Concurrent medication/care: All patients had the same anesthesia protocol. They received 0.1 mg/kg of morphine as premedication. Anesthesia was induced by thiopental (5-7mg/kg) and atracurium (0.5 mg/kg) afterwards. Maintenance of anesthesia was done with isoflurane (proportionate to the patients' hemodynamic status), N2O (50%) and O2 (50%).. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain (VAS) at 4 hours at 4 hours; Group 1: mean 45.6 (SD 16.6); n=20, Group 2: mean 80 (SD 12.6); n=20; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5
- Actual outcome: pain (VAS) at 24 hours at 24 hours; Group 1: mean 24.8 (SD 10.4); n=20, Group 2: mean 46 (SD 9.6); n=20; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: cumulative morphine consumption 48 hours at 48 hours; Group 1: mean 3 mg (SD 2); n=20, Group 2: mean 17.8 mg (SD 9.2); n=20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: nausea+vomiting at 48 hours; Group 1: 3/20, Group 2: 3/20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Leal 2013[577]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Brazil; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	40 patients over 18 years of age, both sexes, ASA I or II, undergoing video laparoscopic cholecystectomy. Patients were allocated into two equal groups.
Exclusion criteria	not specified
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): ketamine 46(12.5); control 45.5 (16.1). Gender (M:F): 7/33. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (laparoscopic cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. G1 received remifentanil (0.4 mcg.kg-1.min-1) and ketamine (5 mcg.kg-1.min-1). Remifentanil was increased or decreased as needed, based on hemodynamic data (hypotension, defined as systolic blood pressure below 80 mm Hg or mean arterial blood pressure below 60 mm Hg). Infusion of solutions was maintained until wound closure. Atracurium doses were titrated to maintain muscle relaxation. Postoperative pain was treated with morphine via patient controlled analgesia (PCA) by intravenous route, with bolus of 2 mg in 3 mL, 10 minutes safety interval (administration blockade), dose limit of 20 mg in four hours, and without infusion.. Duration intraop + post op. Concurrent medication/care: Infusion was administered with midazolam (3 mg, 30 min), remifentanil (1 mcg.kg-1), propofol (2-4 mg.kg-1), and atracurium (0.5 mg.kg-1). Anesthesia was maintained with sevoflurane and 50% oxygen without nitrous oxide. Before extubation, atropine (0.02 mg.kg-1), neostigmine (0.04 mg.kg-1),metoclopramide (20 mg), and ondansetron (4 mg) were administered. Morphine (0.1mg.kg-1) was administered at the end of surgery.

	. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. G2 received remifentanil (0.4 mcg.kg-1.min-1) and saline (0.9%). Remifentanil was increased or decreased as needed, based on hemodynamic data (hypotension, defined as systolic blood pressure below 80 mm Hg or mean arterial blood pressure below 60 mm Hg). Infusion of solutions was maintained until wound closure. Atracurium doses were titrated to maintain muscle relaxation. Postoperative pain was treated with morphine via patient controlled analgesia (PCA) by intravenous route, with bolus of 2 mg in 3 mL, 10 minutes safety interval (administration blockade), dose limit of 20 mg in four hours, and without infusion.. Duration intraop+ post op. Concurrent medication/care: Infusion was administered with midazolam (3 mg, 30 min), remifentanil (1 mcg.kg-1), propofol (2-4 mg.kg-1), and atracurium (0.5 mg.kg-1). Anesthesia was maintained with sevoflurane and 50% oxygen without nitrous oxide. Before extubation, atropine (0.02 mg.kg-1), neostigmine (0.04 mg.kg-1),metoclopramide (20 mg), and ondansetron (4 mg) were administered. Morphine (0.1mg.kg-1) was administered at the end of surgery. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS at 6 hours at at 6 hours; Group 1: mean 0.9 (SD 1.2); n=20, Group 2: mean 0.5 (SD 0.9); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VRS at 24 hours at at 24 hours; Group 1: mean 1.5 (SD 1.3); n=20, Group 2: mean 0.5 (SD 0.7); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Additional morphine consumption at post op; Group 1: mean 29 mg (SD 18.4); n=20, Group 2: mean 25.1 mg (SD 13.3); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at post op; Group 1: 18/20, Group 2: 15/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at post op; Group 1: 12/20, Group 2: 4/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Sahin 2004[1091]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in Turkey; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	47 ASA 1nd 2 patients scheduled for lumbar discectomy.
Exclusion criteria	patients suffering from chronic pain of any origin, regular use of analgesics, opioid use at least 12 hours prior to the operation, drug or alcohol abuse, obesity and psychiatric disorders.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Remifentanil 48.3(11.2); Remifentanil+ketamine 46.5(7.3); placebo 46.1(13.3). Gender (M:F): 24/23. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: Not applicable (Lumbar discectomy).
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. remifentanil infusion of 0.1µg kg-1 min-1 + ketamine 0.5 mgkg-1 with the induction.Postoperative morphine was used PCA with the loading dose of 1 mg with a lockout interval of 15 min. Duration 24 h post op. Concurrent medication/care: Anesthesia was induced with propofol 2mg kg-1 and vecuronium bromide 0.1mg kg-1.. Indirectness: No indirectness (n=14) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. bolus of the same volume saline. Postoperative morphine was used PCA with the loading dose of 1 mg with a lockout interval of 15 min. Duration 24 h post op. Concurrent medication/care: Anesthesia was induced with propofol 2mg kg-1 and vecuronium bromide 0.1mg kg-1.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO	

Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain VAS at 1 hour at 1 h; Reported in the graph only Ketamine group~5; control group~3; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Total morphine consumption at 24 h; Group 1: mean 20.28 mg (SD 11.81); n=17, Group 2: mean 17.93 mg (SD 12.02); n=14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Cengiz 2014[152]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Turkey; Setting: Ankara Numune Training and Research Hospital, Turkey
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients aged 18 - 65 years, ASA grade I, II or III, who were scheduled for total knee arthroplasty surgery under general anesthesia.
Exclusion criteria	allergy to ketamine, a severe cardiovascular disorder (ejection fraction < 30%), renal insufficiency (creatinine clearance < 30 mL/min), an inability to understand the use of patient-controlled analgesia (PCA), a rejection to receive general anesthesia, or a willingness to receive regional anesthesia.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 58 (10). Gender (M:F): 16/44. Ethnicity: NA
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 or 2). 3. Type of surgery: ortho/large joint replacement (TKA).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. racemic ketamine (6 µg/kg/minute) immediately after orotracheal intubation continuing until wound closure. Ten minutes before wound closure, all patients received 5 mg of morphine. Analgesia in the PACU was initially provided via titrating morphine in increments of 3 mg every 5 minutes until the VAS pain score was ≤ 3 cm. Patients were also given. access to a PCA device set to deliver 1-mg boluses of intravenous (IV) morphine, with a lockout period of 5 minutes and no background infusion or limits.. Duration intraoperative. Concurrent medication/care: As additional analgesia; all patients were ordered 1000 mg paracetamol intravenously, every 8 hours for 24 hours, to be administered. Patients received 4 mg ondansetron if they complained of nausea and vomiting.. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Similar volume of saline (placebo)

	immediately after orotracheal intubation continuing until wound closure. Ten minutes before wound closure, all patients received 5 mg of morphine. Analgesia in the PACU was initially provided via titrating morphine in increments of 3 mg every 5 minutes until the VAS pain score was ≤ 3 cm. Patients were also given. access to a PCA device set to deliver 1-mg boluses of intravenous (IV) morphine, with a lockout period of 5 minutes and no background infusion or limits.. Duration intraoperative. Concurrent medication/care: As additional analgesia; all patients were ordered 1000 mg paracetamol intravenously, every 8 hours for 24 hours, to be administered. Patients received 4 mg ondansetron if they complained of nausea and vomiting.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain (VAS) at 6 hours; Group 1: mean 0.9 (SD 0.66); n=30, Group 2: mean 2.1 (SD 0.8); n=30; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain (VAS) at 24 hours; Group 1: mean 0.2 (SD 0.48); n=30, Group 2: mean 0.63 (SD 0.61); n=30; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Cumulative morphine consumption (mg) at 6 hours; Group 1: mean 28.73 mg (SD 11.88); n=30, Group 2: mean 55.76 mg (SD 12.56); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Cumulative morphine consumption (mg) at 24 hours; Group 1: mean 47 mg (SD 15.3); n=30, Group 2: mean 85.2 mg (SD 8.01); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at 24 hours; Group 1: 7/30, Group 2: 14/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

- Actual outcome: Vomiting at 24 hours; Group 1: 1/30, Group 2: 5/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Edwards 1993[261]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in United Kingdom; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	40 patients aged greater than 60 years old undergoing elective upper abdominal surgery
Exclusion criteria	not stated
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine group 71.33(6.574) control - 68(8). Gender (M:F): 19/21. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (upper abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine group: morphine 1 mg.h-lplus ketamine (5 mg.h-'; group 3, 10 mg.h-'; and 20 mg.h-') Immediately after surgery, each patient was connected to a Graseby patient-controlled analgesia (PCA) infusion pump, which was programmed to deliver a 1 mg bolus of morphine with a lockout time of 5 min. This

	was used by the patient throughout the study period as a measure of adequacy of the infusion and to ensure that adequate analgesia was available. . Duration intra+postop. Concurrent medication/care: Premedication was with temazepam 10 or 20 mg orally, 1 h prior to induction. Anaesthesia was induced with fentanyl (2 pg.kg-'), a sleep dose of thiopentone, and vecuronium (0.1 mg.kg-'). Following tracheal intubation, the lungs were ventilated with oxygen, nitrous oxide and enflurane 1-2%. Muscle relaxation was maintained throughout the operation with intermittent increments of vecuronium. At the end of the procedure, neuromuscular blockade was reversed with neostigmine (2.5 mg) and glycopyrronium(0.5 mg). . Indirectness: No indirectness (n=10) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. control group: morphine 1 mg.h-Immediately after surgery, each patient was connected to a Graseby patient-controlled analgesia (PCA) infusion pump, which was programmed to deliver a 1 mg bolus of morphine with a lockout time of 5 min. This was used by the patient throughout the study period as a measure of adequacy of the infusion and to ensure that adequate analgesia was available. . Duration intra+postop. Concurrent medication/care: Premedication was with temazepam 10 or 20 mg orally, 1 h prior to induction. Anaesthesia was induced with fentanyl (2 pg.kg-'), a sleep dose of thiopentone, and vecuronium (0.1 mg.kg-'). Following tracheal intubation, the lungs were ventilated with oxygen, nitrous oxide and enflurane 1-2%. Muscle relaxation was maintained throughout the operation with intermittent increments of vecuronium. At the end of the procedure, neuromuscular blockade was reversed with neostigmine (2.5 mg) and glycopyrronium(0.5 mg). . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Pain none (number of patients) 4 hours at 4 hours; Group 1: 0/24, Group 2: 0/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1

- Actual outcome: Pain mild (number of patients) 4 hours at 4 hours; Group 1: 13/24, Group 2: 0/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1
- Actual outcome: Pain moderate (number of patients) 4 hours at 4 hours; Group 1: 10/24, Group 2: 5/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1
- Actual outcome: Pain severe (number of patients) 4 hours at 4 hours; Group 1: 6/24, Group 2: 4/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1
- Actual outcome: Pain very severe (number of patients) 4 hours at 4 hours; Group 1: 1/24, Group 2: 1/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1
- Actual outcome: Pain none (number of patients) 24 hours at 24 hours; Group 1: 11/24, Group 2: 2/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1
- Actual outcome: Pain mild (number of patients) 24 hours at 24 hours; Group 1: 10/24, Group 2: 3/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1
- Actual outcome: Pain moderate (number of patients) 24 hours at 24 hours; Group 1: 3/24, Group 2: 4/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1
- Actual outcome: Pain severe (number of patients) 24 hours at 24 hours; Group 1: 0/24, Group 2: 0/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1
- Actual outcome: Pain very severe (number of patients) 24 hours at 24 hours; Group 1: 0/24, Group 2: 0/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: amount of PCA morphine used at 24 hours; Mean (range)
control group - 47.7(16-99); ketamine 5 - 35.1(15-64); ketamine10 - 43.2 (18-87); ketamine20-36.3(18-55);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 1

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: respiratory depression at 24 hours; Group 1: 1/30, Group 2: 3/10
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Kotsovolis 2015[551]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=148)
Countries and setting	Conducted in Greece; Setting: University hospital and Military hospital in Thessaloniki
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	ASA 1 and 2; age 18-79 years undergoing Laparoscopic Cholecystectomy.
Exclusion criteria	Chronic use of benzodiazepines; opioids; barbiturates; antiseizure medication and any type of antidepressants; history of allergic reaction to any of the analgesics used in this study; history of gastric or duodenal ulcer; history of aspirin-induced asthma, any preoperative laboratory finding of potential hepatic,renal or coagulation dysfunction. History of increased intraocular prssure; and history of uncontrolled hypertension
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Other: Mean(no SD) ketamine44.88; placebo 53.13. Gender (M:F): ketamine 8/17; placebo6/18. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (Laparoscopic Cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine group patients were administered 0.3mg/kg ketamine. in the recovery room a PCA pump was applied. the pump contained 50 mg of morphine at concentration of 1 mg/mL. the bolus dose was set to 1 mg, and the lockout time was 10 min. In cases of supplementary analgesia 1000 mg paracetamol was administered.. Duration 36 hours. Concurrent medication/care: General anesthesia was induced with 3 µg/kg fentanyl, 2mg/kg propofol and 0.2 mg cisatracurium and maintained using inhale sevoflurane. Indirectness: No indirectness (n=28) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Placebo group received only placebo. In cases of supplementary analgesia 1000 mg paracetamol was administered.. Duration 36 h. Concurrent medication/care: General anesthesia was induced with 3 µg/kg fentanyl, 2mg/kg propofol and 0.2 mg cisatracurium and maintained using inhale sevoflurane. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain NRS (Cholelithiasis-related) at post op 24 h; No SD Ketamine group - 4.2; Placebo group - 5.96; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Mean total morphine consumption 24 h at post op 24 h; Mean; , Units: mg, Comments: Mean (no SD) Ketamine group - 22.38; Placebo group - 20.29; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4 - Actual outcome: Mean cumulative morphine consumption at 6 h at post op 6 h; reported in the graph only (no SD) Ketamine group ~14; Placebo group ~12; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4 - Actual outcome: Mean cumulative morphine consumption at 24 h at post op 24 h; reported in the graph only (no SD) Ketamine group ~22; Placebo group ~20; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea + vomiting at 24 h at post op 24 h; Group 1: 15/25, Group 2: 19/24 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Javery 1996[441]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in USA; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Following approval of the University of Kentucky Medical Institutional Review Board, 42 ASA 1 and 2 patients between the ages of 21 and 55 yr who were to undergo elective lumbar microdiscectomy gave informed consent before electing to participate in the study
Exclusion criteria	not specified
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): MK - 37.3 (9.9); Morphine 39.5(7.2). Gender (M:F): morfine + ketamine 79% male; Morphine group 88% male. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: ortho/large joint replacement (microdiscectomy).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. IVPCA consisting of morphine with ketamine 1 mg. m1-1 of each. BARD ambulatory IVPCA pumps were programmed to deliver 1 ml of solution with a lockout of six minutes. No basal infusion was used. No supplemental analgesia or sedation was administered to the patients during their postsurgical hospital stay.. Duration 24 hours post op. Concurrent medication/care: Patients were pre-medicated in the holding area with midazolam, up to 0.05 mg- kg -1 iv. No preoperative opioids or nonsteroidal medications were used. General anaesthesia was induced with thiopentone 5 mg.kg -1 and tracheal intubation was facilitated with succinylcholine 1.5 mg. kg -1. Patients were allowed to receive fentanyl up to 2 ktg. kg -1 within 20 min after intubation. Anaesthesia was maintained with isoflurane and 100% oxygen with vecuronium bromide for muscle relaxation during the remainder of the case.. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. IVPCA consisting of morphine 1 mg. m1-1. BARD ambulatory IVPCA pumps were programmed to deliver 1 ml of solution with a lockout of six

	minutes. No basal infusion was used. No supplemental analgesia or sedation was administered to the patients during their postsurgical hospital stay.. Duration 24 hours post op. Concurrent medication/care: Patients were pre-medicated in the holding area with midazolam, up to 0.05 mg- kg -1 iv. No preoperative opioids or nonsteroidal medications were used. General anaesthesia was induced with thiopentone 5 mg.kg -1 and tracheal intubation was facilitated with succinylcholine 1.5 mg. kg -1. Patients were allowed to receive fentanyl up to 2 ktg. kg -1 within 20 min after intubation. Anaesthesia was maintained with isoflurane and 100% oxygen with vecuronium bromide for muscle relaxation during the remainder of the case.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: pain at 24 hours at post op; Group 1: mean 2.3 (SD 1.67); n=22, Group 2: mean 4.5 (SD 1.54); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: morphine consumption 24 h at post op; Group 1: mean 25.82 (SD 16.4); n=22, Group 2: mean 51.1 (SD 20.8); n=20; Comments: p<0.001
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: nausea at post op; Group 1: mean 1.39 (SD 0.755); n=22, Group 2: mean 2.2 (SD 1.196); n=20
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Garg 2016[320]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in India; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	66 ASA 1 and 2 patients aged 18 to 60, scheduled to undergo selective spine surgery.
Exclusion criteria	Patients with hypertension, coronary heart disease, heart block and patients on alpha2 agonist or beta blockers were excluded
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine 36.45(13.39) control 36.32(14.32). Gender (M:F): ketamine group 13/9/ control group 16/6. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: Not applicable (elective spine surgery).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients in ketamine group received a bolus of ketamine 0.25 mg/kg, followed by infusion at the rate 0.25 mg/kg/h. These patients also received midazolam 10µg/kg bolus followed by 10 µg/kg/h infusion through the same infusion pump. At pain score (NRS 4 or more) iv morphine 3 mg bolus was administered as rescue analgesic drug. Duration 24 hours. Concurrent medication/care: All patients received a balanced analgesia, propofol, vecuronium for induction, followed by maintenance with propofol, oxygen and nitrous oxide.. Indirectness: No indirectness (n=22) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients in placebo group received volume matched bolus and infusion of 0.9% saline. At pain score (NRS 4 or more) iv morphine 3 mg bolus was administered as rescue analgesic drug. Duration 24 hours. Concurrent medication/care: All patients received a balanced analgesia, propofol, vecuronium for induction, followed by maintenance with propofol, oxygen and nitrous oxide.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS at 6 hours at 6 hours; Median (interquartile range)
Ketamine - 2(2-3); control 6(4.75-7);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0
- Actual outcome: Pain VRS at 24 hours at 24 hours; Median (interquartile range)
Ketamine - 2(1-3); control 4(3-4.25);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Rescue morphine in first 24 hours at 24 hours; Group 1: mean 2.45 mg (SD 2.067); n=22, Group 2: mean 15.64 mg (SD 9.31); n=22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Vomiting + nausea 48hours at 48hours; Group 1: 3/22, Group 2: 1/22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Yamauchi 2008[1384]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=202)
Countries and setting	Conducted in Japan; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	202 patients ASA physical status I or II, aged 20–70 yr, and undergoing posterior cervical or lumbar spinal surgery were prospectively randomized
Exclusion criteria	Exclusion criteria included chronic pain syndrome, history of opioid or steroid use, and severe surgical area pain
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine 60.16(17.06); control 57(17.45). Gender (M:F): Cervical surgery. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: Not applicable (Posterior cervical or lumbar spinal surgery).
Indirectness of population	--
Interventions	(n=133) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. ketamine 1 mg/kg followed by 42 or 83 µg kg-1 h-1, Postoperative patient controlled analgesia fentanyl was administered with a background infusion. The PCA was programmed to deliver 0.5 µg kg-1 h-1 of fentanyl on basal infusion and 0.5 µg/kg on demand with 6 minutes lockout for 48 h. Nonsteroidal antiinflammatory drugs (NSAIDs) (diclofenac suppository 50 mg) were administered at the end of surgery to all patients, and if necessary, patients could freely request NSAIDs every 8 h. . Duration intra+48 post op. Concurrent medication/care: Anesthesia was induced with propofol 2–3 mg/kg and fentanyl 2 µg/kg and maintained by sevoflurane 1–3% and nitrous oxide 60% in oxygen with tracheal intubation. . Indirectness: No indirectness

	(n=67) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group received isotonic saline, Postoperative patient controlled analgesia fentanyl was administered with a background infusion. The PCA was programmed to deliver 0.5 μg kg-1 h-1 of fentanyl on basal infusion and 0.5 μg/kg on demand with 6 minutes lockout for 48 h. Nonsteroidal antiinflammatory drugs (NSAIDs) (diclofenac suppository 50 mg) were administered at the end of surgery to all patients, and if necessary, patients could freely request NSAIDs every 8 h. . Duration intraop+48 hours post op. Concurrent medication/care: Anesthesia was induced with propofol 2–3 mg/kg and fentanyl 2 μg/kg and maintained by sevoflurane 1–3% and nitrous oxide 60% in oxygen with tracheal intubation.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 6 hours at at 6 hours; Reported in the graph only
Ketamine group(42μg)~25; Ketamine(83 μg)~2; control~25;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Pain VAS at 24 hours at at 24 hours; Reported in the graph only
Ketamine group(42μg)~15; Ketamine(83 μg)~2; control~20;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: total fentanyl consumption post op at 6 hours at at 6 hours; Reported in the graph only
Ketamine group(42μg)~8; Ketamine(83 μg)~6; control~9;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: total fentanyl consumption post op at 24 hours at at 24 hours; Reported in the graph only
Ketamine group(42μg)~15; Ketamine(83 μg)~12; control~16;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea and vomiting at 48 h; Group 1: mean 1.161 (SD 1.241); n=133, Group 2: mean 1.5 (SD 1.959); n=67
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Times of NSAID requirement mean at 48 h; Group 1: mean 1.573 (SD 0.936); n=133, Group 2: mean 2.325 (SD 0.603); n=67 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Dahi-taleghani 2014[212]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=140)
Countries and setting	Conducted in Iran; Setting: University Hospital
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All male patients, aged 18-65 years undergoing orthopedic surgery with history of opium abuse. ASA 1-2
Exclusion criteria	female gender, other anesthetic methods (except for general anesthesia), ASA class more than III, duration of anesthesia less than one hour, other routes of drug abuse (except for inhalational opium for two years), and patient's refusal to continue the study after primary approval for study entry.
Recruitment/selection of patients	Not reproted
Age, gender and ethnicity	Age - Mean (SD): 39 (7). Gender (M:F): all male. Ethnicity: NA 1
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 3. Type of surgery: ortho/large joint replacement
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. a combined solution of 1 mg/mL ketamine and 0.5 mg/mL morphine was prepared as the PCA analgesia protocol. This was started immediately in the postoperative period, at 10 minutes intervals, and each bolus contained 2 mL of the solution.. Duration n/a. Concurrent medication/care: Anesthesia was induced using 0.2 mg/ Kg IV midazolam, 200 µg fentanyl, 5 mg/Kg sodium thiopental, and 5 mg/Kg atracurium.. Indirectness: No indirectness (n=70) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. A combination of morphine (0.5 mg/mL) plus normal saline solution. PCA analgesia was started immediately in the postoperative period at 10 minutes intervals, using 2 mL of the solution in each PCA bolus. . Duration n/a. Concurrent medication/care: Anesthesia was induced using 0.2 mg/Kg IV midazolam, 200 µg fentanyl, 5 mg/Kg sodium thiopental, and 5 mg/Kg atracurium.. Indirectness: No indirectness

Funding	Academic or government funding (Anesthesiology Research Center)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain (VAS) at 6 hours; Group 1: mean 1.5 (SD 0.8); n=70, Group 2: mean 2.2 (SD 1.1); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0
- Actual outcome: Pain (VAS) at 24 hours; Group 1: mean 1 (SD 0.5); n=70, Group 2: mean 1.7 (SD 0.8); n=70; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: total morphine dose at 24 hours; Group 1: mean 12 mg (SD 3); n=70, Group 2: mean 7 mg (SD 2); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at 24 hours; Group 1: 10/70, Group 2: 4/70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Vomiting at 24 hours; Group 1: 6/70, Group 2: 1/70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	D'alonzo 2011[211]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=41)
Countries and setting	Conducted in USA; Setting: Duke University Medical Center, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not specified
Exclusion criteria	Aged less than 18 years, recent myocardial infarction (within 6 months), a history of psychotic disorder, uncontrolled hypertension, allergy to ketamine, an acute intracranial process, or evidence of uncontrolled intracranial or intraocular hypertension.
Recruitment/selection of patients	undergoing lobectomy by video assisted thoracoscopic surgery or open thoracotomy
Age, gender and ethnicity	Age - Mean (SD): Ketamine: 61 ± 12; Opioid: 66 ± 10. Gender (M:F): 17/23. Ethnicity: NA
Further population details	1. Age: >60 years (Ketamine: 61 ± 12; Opioid: 66 ± 10). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (video assisted thoracoscopic surgery or open thoracotomy).
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. receive 0.5 mg/kg of intravenous ketamine intravenously prior to chest wall incision. Duration Preoperatively. Concurrent medication/care: Intraoperatively: Fentanyl, Hydromorphone and Remifentanil Postoperatively: Ketorolac (dose not specified) & Epidural (medications not specified). Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Normal saline equivalent of Ketamine bolus. Duration preoperatively. Concurrent medication/care: Intraoperatively: Fentanyl, Hydromorphone and Remifentanil Postoperatively: Ketorolac (dose not specified) & Epidural (medications not specified). Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score 4 hours at < 6 hours postoperatively; Group 1: mean 3.8 pain score (SD 2.1); n=20, Group 2: mean 3.1 pain score (SD 2.8); n=20; pain scale 0-10 Top=High is poor outcome; Comments: p value 0.20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: protocol deviation; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 24 hours at 24 hours postoperatively; Group 1: mean 2.6 (SD 2.2); n=20, Group 2: mean 2.8 (SD 2.1); n=20; Pain scale 0-10 Top=High is poor outcome; Comments: p value 0.37
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: protocol deviation; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Additional Ketorolac given at 24 hours postoperatively; Group 1: 12/20, Group 2: 10/20; Comments: p value 0.75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: protocol deviation; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Dahl 2000[214]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=99)
Countries and setting	Conducted in USA; Setting: Elective surgery; secondary care
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 96 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult women, ASA physical status I–III, undergoing elective abdominal hysterectomy procedures.
Exclusion criteria	patients requiring chronic analgesic medication, having psychological disorders, and having a history of drug or alcohol abuse.
Recruitment/selection of patients	elective patients recruited
Age, gender and ethnicity	Age - Mean (SD): 49 (6). Gender (M:F): Define. Ethnicity: NA
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1-3 included). 3. Type of surgery: gynae-oncology
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. ketamine 0.4 mg/kg IV before the start of surgery and saline at the end of surgery or saline at the start of surgery and ketamine 0.4 mg/kg IV at the end of surgery. The rescue analgesic, ketobemidone, was given in incremental doses of 1mg IV when the pain score was greater than 30mmon the VAS. . Duration perioperative. Concurrent medication/care: All patients were given acetaminophen 1 g sup three times daily.. Indirectness: No indirectness (n=29) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. saline at the start of surgery and saline at the end of surgery. The rescue analgesic, ketobemidone, was given in incremental doses of 1mg IV when the pain score was greater than 30mmon the VAS. . Duration Perioperative. Concurrent medication/care: All patients were given acetaminophen 1 g sup three times daily.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO	

Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain (VAS) at 6 hours; Group 1: mean 3.6 (SD 1.42); n=60, Group 2: mean 4.1 (SD 1.6); n=29; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Pain (VAS) at 24 hours; Group 1: mean 5.45 (SD 2.2); n=60, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: Ketobemidone (mg) at 6 hours; Group 1: mean 13.94 mg (SD 6.79); n=60, Group 2: mean 15.1 mg (SD 6.5); n=29 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Ketobemidone (mg) at 24 hours; Group 1: mean 19.2 (SD 6.4); n=60, Group 2: mean 20.4 (SD 8); n=29 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Duale 2009[254]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=86)
Countries and setting	Conducted in France; Setting: Tertiary Hospital, France
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	20-75 years of age scheduled for elective partial pneumonectomy under thoracotomy
Exclusion criteria	Patient refusal, previous thoracic chronic pain, previous neuropathic pain, anaglesic treatment (opiates, TCA's, Venlafaxine, gabapentin or pregabalin, clonazepam, carbemazepine, NMDA-R blockers), contraindication to bupivacaine, morphine, paracetamol, nefopam or ketamine, emergency surgery, poor physical status, advanced cancer, predicted use of epidural anesthesia or paravertebral block.
Recruitment/selection of patients	scheduled for elective partial pneumonectomy under thoracotomy
Age, gender and ethnicity	Age - Mean (SD): Ketamine 61.9 ± 8.3; Placebo: 58.5 ± 8.5 . Gender (M:F): 60/26. Ethnicity: NA
Further population details	1. Age: >60 years (Ketamine 61.9 ± 8.3; Placebo: 58.5 ± 8.5). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (partial pneumonectomy under thoracotomy).
Indirectness of population	--
Interventions	(n=42) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine was diluted to 500mg in 500ml in isotonic saline (1mg = 1ml). Then 1ml/Kg of the solution was given 5 minutes before the surgical incision, and 1ml/Kg-1 until skin closure. For the Postoperative period 1mg/Kg-1 of ketamine was diluted in isotonic saline in a 48ml- syringe then infused at the rate of 2mL/hour -1 (1mg/kg-1 for 24h), then discontinued. . Duration intraoperatively to postoperative. Concurrent medication/care: In addition to the intraoperative ropivacaine infiltration, post-operative analgesia was ensured with interpleural 0.2% ropivacaine (40ml into the chest tube clamped for 20 minutes), IV paracetamol (1g every 6 hours), nefopam (80mg per 24h in continuous infusion) and morphine (5mg IV until pain score below 3/10; then delivered via PCA 1mg per ml of isotonic saline; bolus = 1mL, refractory period = 6 minutes, maximal dose = 12mg per 4 hours, no continuous infusion)

	(n=44) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Isotonic Saline was given in the same protocol as Ketamine. (Ketamine 1ml/Kg of the solution was given 5 minutes before the surgical incision, and 1ml/Kg-1 until skin closure. For the Postoperative period 1mg/Kg-1 of ketamine was diluted in isotonic saline in a 48ml- syringe then infused at the rate of 2mL/hour -1 (1mg/kg-1 for 24h), then discontinued). Duration intraoperatively to postoperative. Concurrent medication/care: In addition to the intraoperative ropivacaine infiltration, post-operative analgesia was ensured with interpleural 0.2% ropivacaine (40ml into the chest tube clamped for 20 minutes), IV paracetamol (1g every 6 hours), nefopam (80mg per 24h in continuous infusion) and morphine (5mg IV until pain score below 3/10; then delivered via PCA 1mg per ml of isotonic saline; bolus = 1mL, refractory period = 6 minutes, maximal dose = 12mg per 4 hours, no continuous infusion)
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain (area under curve) at 24 hours postoperatively; Area under the curve: Ketamine: 73 ± 40; Opioid: 88 ± 34, Comments: p value = 0.039);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: conversion surgery, early reoperation, missed information for investigator.; Group 2 Number missing: 3, Reason: ICU admission, conversion surgery, early reoperation

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine consumption at 24 hours postoperatively; Mean; (Median (IQR): Ketamine: 37mg (24-49); Opioid: 41mg (32-59)) milligrams, Comments: p value = 0.068);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: conversion surgery, early reoperation, missed information for investigator.; Group 2 Number missing: 3, Reason: ICU admission, conversion surgery, early reoperation

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at postoperatively; Group 1: 19/39, Group 2: 15/41; Comments: p value 0.482
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: conversion surgery, early reoperation, missed information for investigator.; Group 2 Number missing: 3, Reason: ICU admission, conversion surgery, early reoperation
- Actual outcome: Vomiting at postoperatively; Group 1: 3/39, Group 2: 0/41; Comments: p value 0.117
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: conversion surgery, early reoperation, missed information for

investigator.; Group 2 Number missing: 3, Reason: ICU admission, conversion surgery, early reoperation	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Nourozi 2010[928]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Iran; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Hundred patients aged 15-60 years who were candidates for elective major abdominal operations were enrolled into the study
Exclusion criteria	Exclusion criteria included patient refusal for participating in the study, chronic pain, chronic opioid consumption, drug or alcohol abuse and contraindication for ketamine or pethidine. Thus patients with history of cardiovascular disease. allergy to study drugs, hypertension, pheuchromocytoma, psychological disorders, loss of conciousness, seizure or renal diseases were excluded.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Pethidine+ketamine-43.18 (13.24); Pethidine 39.3(17.76. Gender (M:F): 36/64. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (Major abdominal operations).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. IV administration of drugs was done in the post anesthesia care unit immediately after awakening the patient when he/she was conscious. prescribed regimen was 5 mg pethidine and 0.25mg kg-1 ketamine. Duration postoperatively. Concurrent medication/care: On arrival in the operation room,an intravenous line was set up and patients were premedicated with 2.5 µg kg-'Fentanyl (Aborayhan Co.,Tehran, Iran) and 0.03 mg kg-' midazolam (Tehran Kimia Co.,Tehran, Iran) intravenously before induction ofanesthesia. After 3 min ofpre-oxygenation with oxygen100%, general anesthesia was induced with incremental doses of sodium thiopentone (Sandoz, France) up to 5 mgkg-1 untildisappearance of the ciliary reflex under standard monitoring. To facilitatelaryngoscopy and endotracheal intubation, 0.5 mg kg-1 Atracuronium (AborayhanCo., Tehran, Iran) was used. Three minutes later, laryngoscopy using Macintosh blade size 3 and intubation using

	intratracheal tube (size 7 .5-8) were erformed by an anesthesiologist. After that, anesthesia was maintained with 1-1.5 1v1AC (inspiratory saturation) of Halothane in 0 2 and N20 (50% mixture). Atracuronium 0.2 mg kg-1was used for maintenance of neuromuscular blockade. Fentanyl 3 µg kg-1 was given before skin incision, with additional doses as required. The patients were ventilated mechanically with tidal volwne of 10-15 mg kg-1 and a respiratory rate of 12 min-1 blockade. Fentanyl 3 µg kg-1 was given before skin incision, with additional doses as required. The patients were ventilated mechanically with tidal volwne of 10-15 mg kg-1 and a respiratory rate of 12 min-1 Atracuronium 0.2 mg kg-1 was used for maintenance of neuromuscular Halothane in 0 2 and N20 (50% mixture). . Indirectness: No indirectness (n=25) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. IV administration of drugs was done in the post anesthesia care unit immediately after awakening the patient when he/she was conscious. prescribed regimen was pethidine 10 mg . Duration postoperatively. Concurrent medication/care: On arrival in the operation room,an intravenous line was set up and patients were premedicated with 2.5 µg kg-'Fentanyl (Aborayhan Co.,Tehran, Iran) and 0.03 mg kg-' midazolam (Tehran Kimia Co.,Tehran, Iran) intravenously before induction ofanesthesia. After 3 min ofpre-oxygenation with oxygen100%, general anesthesia was induced with incremental doses of sodium thiopentone (Sandoz, France) up to 5 mgkg-1 untildisappearance of the ciliary reflex under standard monitoring. To facilitatelaryngoscopy and endotracheal intubation, 0.5 mg kg-1 Atracuronium (AborayhanCo., Tehran, Iran) was used. Three minutes later, laryngoscopy using Macintosh blade size 3 and intubation using intratracheal tube (size 7 .5-8) were erformed by an anesthesiologist. After that, anesthesia was maintained with 1-1.5 1v1AC (inspiratory saturation) of Halothane in 0 2 and N20 (50% mixture). Atracuronium 0.2 mg kg-1was used for maintenance of neuromuscular blockade. Fentanyl 3 µg kg-1 was given before skin incision, with additional doses as required. The patients were ventilated mechanically with tidal volwne of 10-15 mg kg-1 and a respiratory rate of 12 min-1 . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain VAS (graph only) at Please enter a time period.; reported in the graph only
at 6 hours Ketamine group~ 4 Control group~4
at 19 hours Ketamine group~ 1 Control group~1;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Dose of rescue medication (Pethidine) graph only at Please enter a time period.; reported in the graph only at 6 hours Ketamine group~ 1mg Control group~4mg at 19 hours Ketamine group~ 0 Control group~0; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: nausea+vomiting (graph) at Please enter a time period.; reported in the graph only at 6 hours Ketamine group~ 3 Control group~8 at 24 hours Ketamine group~ 0 Control group~1; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Song 2013[1180]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in South Korea; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	The inclusion criteria were non-smoking female patients between 20 and 65 yr of age, who were ASA physical status I or II and undergoing 1–2 level posterior lumbar spinal fusion surgery.
Exclusion criteria	Exclusion criteria were patients with history of receiving anti-emetics within 1 day before surgery, opioid dministration within 1 week of surgery, regular administration of corticosteroids, a history of psychiatric disorder, drug or alcohol abuse, gastrointestinal motility disorder, severe hepatic or renal disease, insulin dependent diabetes, or patients who were admitted to the intensive care unit after operation.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (range): ketamine 57(30-65); control 58 (34-65). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: ortho/large joint replacement (spinal fusion surgery).
Indirectness of population	--
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Immediately after the induction of anaesthesia, 0.3mgkg-1 of ketamine was injected to the patients in the ketamine group, and IV-PCA was commenced. The PCA regimen consisted of fentanyl 20 mg kg-1 and ondansetron 8 mg (total volume including saline: 180 ml) and was programmed to deliver 2 ml h-1 as a background infusion and a bolus of 2 ml on-demand, with a 15 min lockout time during a 48 h period. Ketamine 3 mg kg-1 was mixed to IV-PCA in the ketamine group . Duration intra+post op. Concurrent medication/care: Anaesthesia was induced with propofol 2mgkg-1, remifentanil 1 mg kg-1, and rocuronium 0.8 mg kg-1 and maintained with sevoflurane inhaled at an end tidal concentration of 1.5–2.5% in 50% oxygen/air mixture and 0.1–0.2 mg kg-1 min-1 of remifentanil

	. Indirectness: No indirectness (n=25) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Immediately after the induction of anaesthesia, 0.3mgkg-1 of normal saline was injected to the patients in the control group and IV-PCA was commenced. The PCA regimen consisted of fentanyl 20 mg kg-1 and ondansetron 8 mg (total volume including saline: 180 ml) and was programmed to deliver 2 ml h-1 as a background infusion and a bolus of 2 ml on-demand, with a 15 min lockout time during a 48 h period. Normal saline was mixed to IV-PCA in the control . Duration Intra+post op. Concurrent medication/care: Anaesthesia was induced with propofol 2mgkg-1, remifentanil 1 mg kg-1, and rocuronium 0.8 mg kg-1 and maintained with sevoflurane inhaled at an end tidal concentration of 1.5–2.5% in 50% oxygen/air mixture and 0.1–0.2 mg kg-1 min-1 of remifentanil. Indirectness: No indirectness
Funding	Academic or government funding (department sources)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS 0-6 hours at 6 hours; Group 1: mean 37 (SD 23); n=24, Group 2: mean 38 (SD 21); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome: Pain VAS 6-12 hours at 6-12 hours; Group 1: mean 32 (SD 20); n=24, Group 2: mean 35 (SD 26); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome: Pain VAS 12-24 hours at 12-24 hours; Group 1: mean 25 (SD 18); n=24, Group 2: mean 23 (SD 15); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: cumulative dose of Fentanyl (PCA) ~6hours at ~6 hours; Group 1: mean 143 µg (SD 58); n=24, Group 2: mean 156 µg (SD 90); n=25
Risk of bias: All domain - ; Indirectness of outcome: No indirectness
- Actual outcome: cumulative dose of Fentanyl (PCA) ~24hours at ~24 hours; Group 1: mean 399 µg (SD 147); n=24, Group 2: mean 504 µg (SD 232); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)

- Actual outcome: nausea+vomiting 0-6 hours at on pacu 0-6 hours; Group 1: 13/24, Group 2: 4/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: nausea+vomiting 6-12 hours at on pacu 6-12 hours; Group 1: 11/24, Group 2: 7/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: nausea+vomiting 12-24 hours at on pacu 12-24 hours; Group 1: 7/24, Group 2: 9/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Aubrun 2008[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in France
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Women aged 18-70 yr, ASA 1-2, weighing between 50 and 100 kg, and undergoing elective abdominal gynaecological surgery were included
Exclusion criteria	Preoperative administration of morphine, allergy or contraindication to morphine, ketamine, or NSAIDS, renal failure, hepatic failure, scheduled regional anesthesia, emergency surgery. Patients with delirium or dementia or who were not french speaking and tho who did not understand the pain, mood, memory and cognition scales.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine 50(10); placebo 49(12). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1-2). 3. Type of surgery: gynae-oncology (elective abdominal gynaecologic surgery).
Extra comments	n/a
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. immediately after morphine titration, patients were connected to PCA in the ketamine group patients received combination of Morphine 1mg mL-1 and ketamine 0.5 mg mL-1. lockout period 7 min. Duration 48 h. Concurrent medication/care: patients received oral hydroxyzine (50 or 100 mg) or midazolam (2.5 0r 5 mg) 1 h before surgery. anesthesia was induced with propofol (2.5 mg kg-1) and remifentanil (1µg kg-1) bolus 30-60s followed by an infusion of 0.5 µg kg-1 kg-1 min-1) . Anesthesia was maintained with propofol and remifentanil. Before surgical incision, ketamine 0.15 mg kg-1 aor the same volume of saline was administered iv. 30 min before the end of the operation,0.20 mg kg-1 of morphine and 50 mg of ketoprofen were administered iv. in PACU morphine was titratedusing 3 mg boluses. (n=45) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. immediately after morphine titration,

	patients were connected to PCA in the ketamine group patients received Morphine 1mg mL-1 lockout period 7 min. Duration 48 h. Concurrent medication/care: patients received oral hydroxyzine (50 or 100 mg) or midazolam (2.5 0r 5 mg) 1 h before surgery. anesthesia was induced with propofol (2.5 mg kg-1) and remifentanil (1µg kg-1) bolus 30-60s followed by an infusion of 0.5 µg kg-1 kg-1 min-1) . Anesthesia was maintained with propofol and remifentanil. Before surgical incision, ketamine 0.15 mg kg-1 or the same volume of saline was administered iv. 30 min before the end of the operation,0.20 mg kg-1 of morphine and 50 mg of ketoprofen were administered iv. in PACU morphine was titrate using 3 mg boluses.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 6 hours at 6 h; Ketamine~18; placebo~18;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain VAS at 24 hours at 24 h; ketamine~16; placebo~18;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: PCA morphine dose 24 h at 24 h; Group 1: mean 24.8 (SD 19.2); n=45, Group 2: mean 17.8 (SD 16.4); n=45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea+vomiting at 24 h; Group 1: 23/45, Group 2: 23/45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Murdoch 2002[777]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in United Kingdom; Setting:
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	ASA grade 1 to 2 patients entered the study and underwent elective total abdominal hysterectomy with or without bilateral salping-oopherectomy.
Exclusion criteria	Not specified
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Morphine+ketamine 43.2(6.6); morphine 41.8 (8.8). Gender (M:F): all female. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA1 and 2). 3. Type of surgery: gynae-oncology (Hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. During the procedure, morphine was administered from the patients PCA syringe according to the patients body surface area (10 mg.m-2)If the patient was randomised to receive morphine and ketamine then she would also receive 7.5 mg.m-2 of ketamine. PCA setting was for 1ml bolus, 5-min lockout and a background infusion of 1ml.h-1 If necessary, a bolus from the PCA syringe was given, patients being discharged to the ward when comfortable. Duration intra and post operatively. Concurrent medication/care: Premedication was with diazepam 15-20 mg 1h prior to the surgery. Induction of anaesthesia was achieved with a sleepdose of thiopental and fentanyl 100 µg. Tracheal intubation was facilitated with vecuronium 0.1 mg.kg-1 and droperidol 0.5 mg given as an antiemetic. Anaestesia was maintained with nitrous oxide and isoflurane in oxygen.. Indirectness: No indirectness (n=21) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. During the procedure, morphine was

	administered from the patients PCA syringe according to the patients body surface area (10 mg.m-2). PCA setting was for 1ml bolus, 5-min lockout and a background infusion of 1ml.h-1 If necessary, a bolus from the PCA syringe was given, patients being discharged to the ward when comfortable. Duration intra and postoperatively. Concurrent medication/care: Premedication was with diazepam 15-20 mg 1h prior to the surgery. Induction of anaesthesia was achieved with a sleepdose of thiopental and fentanyl 100 µg. Tracheal intubation was facilitated with vecuronium 0.1 mg.kg-1 and droperidol 0.5 mg given as an antiemetic. Anaestesia was maintained with nitrous oxide and isoflurane in oxygen.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: pain 0-24 hours at 0-24 hours post op; Reported in the graph as proportions (%)
4 hours - score 0 (Ketamine group ~65; control ~70%)
4 hours - score 1 (Ketamine group ~25%; control ~30%)
4 hours - score 2 (Ketamine group ~10%; control ~0%)

24 hours - score 0 (Ketamine group ~70; control ~40%)
24 hours - score 1 (Ketamine group ~30%; control ~50%)
24 hours - score 2 (Ketamine group ~0%; control ~10%);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain number of occasions pain >=2 was recorded at post op 24 hours; Group 1: 26/21, Group 2: 25/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine consumption (mean) at post op 24h; Group 1: mean 67.6 mg (SD 25.1); n=21, Group 2: mean 66.4 mg (SD 17.7); n=21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Bilgen 2012[108]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=140)
Countries and setting	Conducted in Turkey; Setting: Yeditepe University hospital, Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	ASA 1-2 term pregnant, nulliparous women in whom cesarean delivery was indicated
Exclusion criteria	Parturients with pre-eclampsia, cardiovascular problems, allergy of the study medications, chronic preopoerative pain, or regular analgesic use were excluded
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine group 31(3.786); control 32(4). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (Cesarean section).
Indirectness of population	No indirectness
Interventions	(n=105) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine (0.25 mg kg-1 or 0.25 mg kg-1 or 1 mg kg-1). postoperative analgesia was provided with IV Morphine chloride patient controlled analgesia (PCA) at a concentration of 0.5 mg mL-1. The PCa was set to deliver a 1 mg bolus with a 10 min lock out time without basal infusion. Rescue analgesia was provided with intramuscular diclofenac sodium 75 mg every 12 hours as needed in the postoperative period. The PCA device was used for 48 h postoperatively. Duration intraop + 48 hours post operatively. Concurrent medication/care: Following the administration of the study drug, Anesthesia was induced with 2-2.5 mg kg-1 propofol, muscle relaxation was provided by 0.6 mg kg-1 rucuronium.. Indirectness: No indirectness (n=35) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group received 0.9% normal saline. postoperative analgesia was provided with IV Morphine chloride patient controlled analgesia (PCA) at a concentration of 0.5 mg mL-1. The PCa was set to deliver a 1 mg bolus with a 10 min lock out time without basal infusion. Rescue analgesia was provided with intramuscular diclofenac sodium 75 mg every 12 hours as needed in the postoperative period. The PCA device was used for 48 h postoperatively. Duration Intraop + 48 hours postoperatively. Concurrent medication/care: Following the administration of the study drug,

	Anesthesia was induced with 2-2.5 mg kg-1 propofol, muscle relaxation was provided by 0.6 mg kg-1 rucuronium.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain NRS <6 hours at at 6 hours; Median(range)
Ketamine group1(0.25mg) - 0 (0-5); Ketamine group2(0.5mg) - (0-6); Ketamine group3(1mg) - 0(0-8); Control group - 1 (0-6);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain NRS <24 hours at at 24 hours; Median(range)
Ketamine group1(0.25mg) - 0 (0-4); Ketamine group2(0.5mg) - 0 (0-6); Ketamine group3(1mg) - 0(0-5); Control group - 0 (0-5);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Cumulative Morphine consumption 6 hours at at 6 hours; Group 1: mean 23.67 mg (SD 7.782); n=105, Group 2: mean 22 mg (SD 7); n=35
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Cumulative Morphine consumption 24 hours at at 24 hours; Group 1: mean 43 mg (SD 16.58); n=105, Group 2: mean 38 mg (SD 14); n=35
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at 48 hours; Group 1: 6/105, Group 2: 1/35
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Vomiting at 48 hours; Group 1: 2/105, Group 2: 0/35
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom

scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission	

Study	Hong 2011[403]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in South Korea; Setting: Department of anesthesiology and pain medicine
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	patients classified as ASA 1 or 2 scheduled for laparoscopic gynecologic surgery under general anesthesia were the objects of study.
Exclusion criteria	Patients with a history of drug abuse, renal or hepatic diseases and those taking analgesics were excluded.
Recruitment/selection of patients	scheduled for laparoscopic gynecologic surgery under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Ketamine group 38.8 (12.5); control group 37.6(8.5). Gender (M:F): all female. Ethnicity: no specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA 1 and 2). 3. Type of surgery: gynae-oncology (laparoscopic gynecologic surgery).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. The ketamine group (group K, n = 20) was injected with 0.3 mg/kg of ketamine during induction and continuously infused with 3 μg/kg/min of ketamine during surgery.. Duration intraoperatively. Concurrent medication/care: All patients were premedicated with 2 mg of midazolam and 0.2 mg of glycopyrrolate intramuscularly and 20 mg of famotidine intravenously 30 minutes before arriving to the operating room. Ten minutes before surgery ended, PCA was initiated with a 120 ml mixture containing 40 mg of morphine sulfate, 120 mg of ketorolac, and 12 mg of ondansetron. Loading dose was set at 3 ml, with a continuous infusion at 1.5 ml/hr and additional doses of 1.5 ml with a lockout time of 15 minutes. In the recovery room, if the patient sought more pain control or if VAS was above 4, a trained nurse administered additional dosages from the PCA.. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. The control group was injected and infused with normal saline at the same volumes as the ketamine group.. Duration Intraoperatively. Concurrent medication/care: All patients were premedicated with 2 mg of midazolam and 0.2 mg of

	glycopyrrolate intramuscularly and 20 mg of famotidine intravenously 30 minutes before arriving to the operating room. Ten minutes before surgery ended, PCA was initiated with a 120 ml mixture containing 40 mg of morphine sulfate, 120 mg of ketorolac, and 12 mg of ondansetron. Loading dose was set at 3 ml, with a continuous infusion at 1.5 ml/hr and additional doses of 1.5 ml with a lockout time of 15 minutes. In the recovery room, if the patient sought more pain control or if VAS was above 4, a trained nurse administered additional dosages from the PCA.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea & Vomiting at postoperatively; Group 1: 3/20, Group 2: 2/20 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Cagla ozbakis akkurt 2009[139]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Turkey; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	60 ASA1-2 patients scheduled for arthroscopy under spinal anesthesia were enrolled.
Exclusion criteria	Patients with history of chronic pain, long term opioid consumption, long term opioid consumption, hepatic renal, pulmonary ad cardiovascular system disorders were excluded
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Range: control group 31-60, ketamine group 16-65, ketamine+midazolam 18-57. Gender (M:F): 30/30. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1and 2). 3. Type of surgery: ortho/large joint replacement (Arthroscopy).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine group - 0.15mg kg Ketamine and 1 ml saline. VAS score was >4, then 0.4 mg/kg was given intravenously and, if the score did not decrease within 10 minutes, an additional 0.2 mg/kg meperidine was given. The total Meperidine dose did not exceed a maximum of 2 mg/kg in any 4 hours. Duration intraoperatively. Concurrent medication/care: None of the patients were given premedication. All patients received a 10 mL/kg pre-load of ringer lactate solution before subarachnoid block.Spinal anesthesia was induced with 10 mg 0.5 % hyperbaric bupivacaine.. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group received 1mL+1 mL saline. If VAS score was >4, then 0.4 mg/kg was given intravenously and, if the score did not decrease within 10 minutes, an additional 0.2 mg/kg meperidine was given. The total Meperidine dose did not exceed a maximum of 2 mg/kg in any 4 hours. Duration intraoperatively. Concurrent medication/care: None of the patients were given premedication. All patients received a 10 mL/kg pre-load of ringer lactate solution before subarachnoid block.Spinal anesthesia was inducedced with 10 mg 0.5 % hyperbaric bupivacaine..

	Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain VAS at 6 h at 6 hours; Reported in the graph only Ketamine group~1.2; control group~4.4; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Total Meperidine consumption at post operatively; Group 1: mean 22 mg (SD 6); n=20, Group 2: mean 36 mg (SD 11); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Ghazi-saidi 2002[327]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=53)
Countries and setting	Conducted in Iran; Setting: department of anesthesia and intensive care
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	53 ASA physical status I and II women, who were candidates for cesarean section under general anesthesia
Exclusion criteria	Reasons for exclusion included the followings (i) allergy to either of thiopental, ketamine, morphine, (ii) gestational age less than 36 weeks (iii) candidates with fetal distress (iv) candidate for classical cesarean incision
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine 28.66 (5.25), Control- 27.07(3.28). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (cesarean section).
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. preemptive low-dose ketamine (0.2 mg/kg) administered prior to anesthesia The amount of morphine administered was based on the scale of patient's pain score. If the scale was ≤ 3 no morphine was administered. For the scales between 4 and 6, 3 mg and for scales of 7 and above, 5 mg of morphine was administered. . Duration intra+post op. Concurrent medication/care: After preoxygenation, the content of covered syringe was administered intravenously over 20-30 s. Then 5% thiopental (5mg/kg) was administered intravenously over 30 s, followed by succinylcholine 1.5 mg/kg.Aftertracheal intubation, the patients were ventilated with 50% nitrous oxide in oxygen. Halothan 0.5% was added, to maintain the anesthesia. Further neuromuscularblock was maintained by using atracurium as needed. After delivery of thefetus, 5 IU

	oxytocin, 0.1 mg / kg morphine and 1 mg midazolam were given asbolus IV, in addition 10 IU oxytocin infused intravenously. Uterine incision todelivery time was measured in seconds and recorded. APGAR scores at 1 and 5minutes was noted by pediatrician and recorded. At the end of the surgery,neuromuscular blocking was antagonized by neostigmine 2.5 mg and atropine 1.25mg. In the post-anesthesia care unit, patients were observed for anypsychomimetic reaction. On obtaining desirable condition, patients weredischarged to postnatal ward. In the ward patients were observed for hourly respiratory rate and level of consciousness. Each patient was visited by resident blinded to the patient group at 1, 2 ,6 ,12 ,18,24 hrs after surgery and recorded the patient's NRS or FRS and accordingly, administered morphine for control of pain.. Indirectness: No indirectness (n=26) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. standardized general anesthesia(control group= 26 cases) The amount of morphine administered was based on the scale of patient's pain score. If the scale was ≤ 3 no morphine was administered. For the scales between 4 and 6, 3 mg and for scales of 7 and above, 5 mg of morphine was administered. . Duration intra +post op. Concurrent medication/care: After preoxygenation, the content of covered syringe was administered intravenously over 20-30 s. Then 5% thiopental (5mg/kg) was administered intravenously over 30 s, followed by succinylcholine 1.5 mg/kg.Aftertracheal intubation, the patients were ventilated with 50% nitrous oxide in oxygen. Halothan 0.5% was added, to maintain the anesthesia. Further neuromuscularblock was maintained by using atracurium as needed. After delivery of thefetus, 5 IU oxytocin, 0.1 mg / kg morphine and 1 mg midazolam were given asbolus IV, in addition 10 IU oxytocin infused intravenously. Uterine incision todelivery time was measured in seconds and recorded. APGAR scores at 1 and 5minutes was noted by pediatrician and recorded. At the end of the surgery,neuromuscular blocking was antagonized by neostigmine 2.5 mg and atropine 1.25mg. In the post-anesthesia care unit, patients were observed for anypsychomimetic reaction. On obtaining desirable condition, patients weredischarged to postnatal ward. In the ward patients were observed for hourly respiratory rate and level of consciousness. Each patient was visited by resident blinded to the patient group at 1, 2 ,6 ,12 ,18,24 hrs after surgery and recorded the patient's NRS or FRS and accordingly, administered morphine for control of pain.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: mean pain scores (NRS or FRS) at 24 hours at 24 hours; Mean; , Comments: reported in the graph only
Ketamine~3.2, control6.2;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: cumulative morphine consumption 24 hours at 24 hours; Group 1: mean 6.25 mg (SD 3.42); n=27, Group 2: mean 17.73 mg (SD 4.08); n=26 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Miziara 2016[731]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Brazil; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Eligible participants were all patients aged 18–65 years with ASA 1-2.
Exclusion criteria	Exclusion criteria were use of alcohol or illicit drugs, H2 inhibitors, opioids, or calcium channel blockers in the last 10 days, chronic pain,myocardial ischemia, or psychiatric disorders.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Other: not stated. Gender (M:F): no details. Ethnicity: n/a
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (Laparoscopic cholecystectomy).
Indirectness of population	--
Interventions	(n=24) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine group - before surgery, continuous S(+)-ketamine infusion at a rate of 0.3mg·kg−1 ·h−1. Morphine was administered at a dose of 0.05mg·kg−1 when the patient reported pain for the first time and at a dose of 0.025mg·kg−1 on subsequent occasions. . Duration before+post op. Concurrent medication/care: After venipuncture, patients received intravenous parecoxib sodium(40mg). Anesthesia was induced with midazolam at a dose of 0.05mg·kg−1 and target-controlled infusions of propofol (target dose of 3.0 μ·mL−1) and remifentanil (target dose of 6.0 ng·mL−1) using the Marsh pharmacokinetic model with ke0 of 1.21 min−1 and theMinto pharmacokinetic model, respectively.Unconsciousness was determined by loss of corneal and palpebral reflexes and confirmed by a BIS < 50. Rocuronium (0.6mg·kg−1) was then administered. Immediately after tracheal intubation, the target dose of propofol was adjusted to maintain BIS between 35 and 50 and the target dose of remifentanil was reduced to 3 ng·mL−1.

	. Indirectness: No indirectness (n=24) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group equivalent volume of saline at the same rate . Morphine was administered at a dose of 0.05mg·kg−1 when the patient reported pain for the first time and at a dose of 0.025mg·kg−1 on subsequent occasions. . Duration before +post op. Concurrent medication/care: After venipuncture, patients received intravenous parecoxib sodium(40mg). Anesthesia was induced with midazolam at a dose of 0.05mg·kg−1 and target-controlled infusions of propofol (target dose of 3.0 μ·mL−1) and remifentanil (target dose of 6.0 ng·mL−1) using the Marsh pharmacokinetic model with ke0 of 1.21 min−1 and theMinto pharmacokinetic model, respectively.Unconsciousness was determined by loss of corneal and palpebral reflexes and confirmed by a BIS < 50. Rocuronium (0.6mg·kg−1) was then administered. Immediately after tracheal intubation, the target dose of propofol was adjusted to maintain BIS between 35 and 50 and the target dose of remifentanil was reduced to 3 ng·mL−1. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain VNS(Verbal numeric scale) at post op; Median
ketamine - 5.5; Control - 8.5;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Mean Remifentanil Consumption (mcg·kg-1·min-1) at intraoperatively; Group 1: mean 0.17 mcg·kg-1·min-1·kg−1min−1
(SD 0.054); n=21, Group 2: mean 0.0228 mcg·kg-1·min-1·kg−1min−1
(SD 0.042); n=21
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3
- Actual outcome: Morphine consumption in PACU at post op; Group 1: mean 4 mg (SD 2.29); n=21, Group 2: mean 4.3 mg (SD 0.83); n=21
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3
- Actual outcome: Cumulative Morphine consumption <12 hours at post op <12 hour; Group 1: mean 5.2 mg (SD 2.707); n=21, Group 2: mean 7.525 mg (SD 1.872); n=21
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3 - Actual outcome: Mean morphine dose at post op; Group 1: mean 0.75 mg (SD 1.198); n=21, Group 2: mean 1.825 mg (SD 0.689); n=21 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Leal 2015[578]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in Brazil; Setting: Hospital São Paulo/Federal University of São Paulo
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Inclusion criteria were aged ≥18 years, any sex, classified as American Society of Anesthesiologists(ASA)physical statusI or II, and undergoing laparoscopic cholecystectomy at Hospital SãoPaulo/Federal University of São Paulo, from September 2010 to September 2012.
Exclusion criteria	Patients were excluded if they were chronic users of analgesics or had used opioids within 12 hours of surgery; had a history of drug or alcohol abuse or psychiatric disorder; had contraindications to self-administration of opioids (ie, unable to understand the patient-controlled analgesia [PCA] device); or had a contraindication for the use of ketamine, such as a psychiatric disorder,acute cardiovascular disorder, or unstable hypertension.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine - 45.8(13.1); Control - 43.4 (15.9). Gender (M:F): 9/47. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (laparoscopic cholecystectomy).
Extra comments	n/a
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. The patients in group1 (G1)received remifentanil (0.4 µg/kg per minute)and ketamine(5µg/kg per minute) Remifentanil was administered as necessary until skin closure. Neostigmine was used for antagonizing the neuromuscular block. At the end of the operation, 0.1 mg/kgmorphine, 20 mg metoclopramide, and 4.0 mg ondansetron were administered.Postoperative analgesia was achieved with morphine via a PCA device set to deliver 2 mg of morphine as an intravenous bolus with a 10-minute lockout interval; continuous infusion was not allowed.. Duration intraop + 24 hours post op. Concurrent medication/care: Propofol(2-4mg/kg),1 µg/kg remifentanil, and atracurium (0.5mg/kg) were administered for intubation. Atracurium was titrated to maintain muscle relaxation. Anesthesia was maintained with remifentanil,0.8% isoflurane, and 50% oxygen without

	nitrous oxide.Infusion of the solutions was continued until skin closure.. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients in group2 (G2) received remifentanil(0.4 µg/kg per minute)and saline solution. Remifentanil was administered as necessary until skin closure. Neostigmine was used for antagonizing the neuromuscular block. At the end of the operation,0.1 mg/kg morphine, 20 mg metoclopramide, and 4.0 mg ondansetron were administered. Postoperative analgesia was achieved with morphine via a PCAdevice set to deliver 2 mg of morphine as an intravenous bolus with a 10-minute lockout interval; continuous infusion was not allowed.. Duration Intraop + 24 hours post op. Concurrent medication/care: Propofol(2-4mg/kg),1 µg/kg remifentanil, and atracurium (0.5mg/kg) were administered for intubation. Atracurium was titrated to maintain muscle relaxation. Anesthesia was maintained with remifentanil,0.8% isoflurane, and 50% oxygen without nitrous oxide.Infusion of the solutions was continued until skin closure.. Indirectness: No indirectness
Funding	Academic or government funding (grant 2009/53335-4, São Paulo Research Foundation (Fundação de Amparo à Pesquisa do Estado de São Paulo) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain (0-10) at 6 hours
at post op at 6 hours; Group 1: mean 0.9 (SD 1.2); n=28, Group 2: mean 0.7 (SD 1); n=28
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2
- Actual outcome: Pain (0-10) at 24 hours
at post op at 24 hours; Group 1: mean 1.4 (SD 1.5); n=28, Group 2: mean 0.8 (SD 1); n=28
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Dose morphine consumed (mg) at post op 24 hours; Group 1: mean 27.4 mg (SD 18.3); n=28, Group 2: mean 27.7 mg (SD 12.9); n=28
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2
- Actual outcome: Dose of Remifentanil (µg/kg per minute)
at post op 24 hours; Group 1: mean 0.4 µg/kg per minute (SD 0.1); n=28, Group 2: mean 0.4 µg/kg per minute (SD 0.1); n=28
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2

- Actual outcome: Total dose of Remifentanil (mg) at post op 24 hours; Mean; , Comments: Mean (range; minimal value - maximal value) Ketamine group - 3.7 (1.2-7.2); control group - 3.1(1.5 - 7.5); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea at post op ; Group 1: 22/28, Group 2: 21/28 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 - Actual outcome: Vomiting at post op ; Group 1: 16/28, Group 2: 8/28 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Akhavanakbari 2014[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Iran; Setting: department of anesthesiology
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients were ASA physical status I–II, aged 20-60 and underwent orthopedic surgery.
Exclusion criteria	not specified
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Other: not specified. Gender (M:F): not specified. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: ortho/large joint replacement (orthopaedic surgery).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA morphine 0.2 mg/ml + ketamine 1 mg/ml; or morphine 0.1 mg/ml + ketamine 2 mg/ml + ketamine 1 mg/ml . Duration post surgery. Concurrent medication/care: not specified. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. (morphine 0.2 mg/m. Duration post surgery. Concurrent medication/care: not spesified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO	

Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain VAS at 24h at 24 h; Group 1: mean 1.75 (SD 0.444); n=40, Group 2: mean 4 (SD 0.64); n=20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Pain VAS at 6h at 6 h; Group 1: mean 3.175 (SD 0.601); n=40, Group 2: mean 5.1 (SD 0.7); n=20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: rate of narcotic consumption at 48 hours at 48 hours; Group 1: mean 15.53 mg (SD 1.308); n=40, Group 2: mean 27.55 mg (SD 3.2); n=20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Ganne 2005[318]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=62)
Countries and setting	Conducted in France; Setting: Tertiary Hospital, France
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	not specified
Exclusion criteria	history of chronic pain, psychiatric disease, the administration of an opioid within the 48 h before surgery or the inability to understand the use of a patient controlled analgesia (PCA) device.
Recruitment/selection of patients	undergoing elective ENT surgery for cancer
Age, gender and ethnicity	Age - Mean (SD): Ketamine 56.9±9.5; Placebo: 59.3 ±8.9. Gender (M:F): 57/4. Ethnicity: NA
Further population details	1. Age: <60 years (Ketamine 56.9±9.5; Placebo: 59.3 ±8.9). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I - 25; ASA II - 30; ASA III - 5). 3. Type of surgery: Not stated / Unclear (ENT surgery for cancer (radical neck dissection, laryngectomy, hemimandibulectomy)).
Indirectness of population	--
Interventions	(n=31) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. IV ketamine just before induction (0.15milligrams /kg-1) followed by a continuous infusion during anesthesia (2 micrograms/kg-1min-1).. Duration intra-operatively. Concurrent medication/care: Patients were premedicated with hydroxyzine (100 mg) and alprazolam (0.25mg) 1h before anesthesia. One hour before the anticipated end of surgery, patients received i.v. morphine 0.2mgkg-1. Postoperatively, all patients received a multimodal analgesia regimen for 48 h as is routinely used in our institution. The regimen involved i.v. paracetamol 1g every 6h, i.v. methylprednisolone 2mg/kg-1day-1, and PCA-morphine. The PCA device was programmed to deliver a bolus of 1mg of morphine on demand, with a lockout interval of 7 min, and without a background infusion.. Indirectness: No indirectness (n=31) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Saline bolus just before induction and continuous infusion of saline during anesthesia . Duration intra-operatively. Concurrent medication/care: Patients were premedicated with hydroxyzine (100 mg) and alprazolam (0.25mg) 1h before anesthesia. One hour before the anticipated end of surgery, patients received i.v. morphine 0.2mgkg-1. Postoperatively, all

	patients received a multimodal analgesia regimen for 48 h as is routinely used in our institution. The regimen involved i.v. paracetamol 1g every 6h, i.v. methylprednisolone 2mg/kg-1day-1, and PCA-morphine. The PCA device was programmed to deliver a bolus of 1mg of morphine on demand, with a lockout interval of 7 min, and without a background infusion.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Cumulative doses of morphine at 24 hours postoperatively; Group 1: mean 33.3 milligrams (SD 14.9); n=30, Group 2: mean 31.9 milligrams (SD 15.3); n=31; Comments: (including the intra-operative dose and that administered in the recovery room) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: morphine dosing against protocol; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea and Vomiting at Postoperatively; Group 1: 5/30, Group 2: 3/31 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: morphine dosing against protocol; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Song 2014[1181]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in South Korea; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	75 adult women aged between 20 and 60 years were included in the study. ASA 1-2 scheduled to undergo single port-laparoscopic surgery
Exclusion criteria	Patients were ex-cluded from the study if: (1) they had received blood products; (2) they had a history of drug or alcohol abuse;(3) they suffered from psychiatric disorders, acute cardiovascular disorders orunstable hypertension, other respiratory or neuromuscular pa-thology, ormultiple allergies; (4) they had been treated with any analgesic drug within 24h before surgery; (5) they had contrain-dications to the self-administration ofopioids (i.e., were unable to understand the PCA device); (6) they underwentprolonged surgery (more than 4 h).
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine group 48.9 (6.8); Control - 50.05 (6.319). Gender (M:F): All female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (Laparoscopic surgery).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine group - intraoperative remifentanil at 0.3 μg/kg/min plus 0.25 mg/kg ketamine just before incision, followed by a continuous infusion of 5 μg/kg/min ketamine until skin closure. Each patient was treated via PCA pump (Accufuser® WooYoung Medical, Seoul,Korea) with analgesics containing morphine (40 mg), ketorolac (180 mg), andramo-setron (0.6 mg) in normal saline and in a total volume of 100 ml. . This device was set to deliver a basal infusion of 2 ml/h, andbolus doses of 0.5 ml with a 15 min lockout time.. Duration post operatively. Concurrent medication/care: The induction of anesthesia was commenced with a slow (30-60 s) i.v. bolus dose of remifentanil (1 μg/kg), followed by propofol (1-2 mg/kg), and tracheal intubation was facilitated with rocuronium (0.9 mg/kg) in all groups. As mentioned above, the infusion of remifentanil was fixed in all

	groups, and anesthesia was maintained with desflurane at an initial end-tidal concentration of 1 minimum alveolar concentration (MAC) and oxygen-medical air mixture (fraction of oxygen, 50%). During surgery, anesthesia levels were monitored by stepwise titration of the desflurane concentration by 1 vol%, based on hemodynamic changes and targeting a bispectral index (BIS) from 40-60. Our criterion for hemodynamic change was a systolic blood pressure that exceeded values between ± 20% of pre-induction values. Patients received 10 mg i.v. bolus doses of ephedrine in cases of persistent hypotension. If heart rate decreased to less than 50 beats/min, a 0.5 mg i.v. atropine bolus was administered intrave-nously. Indirectness: No indirectness (n=50) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group - intraoperative remifentanil at 0.1 μg/kg/min or 0.3 μg/kg/min just before incision. Each patient was treated via PCA pump (Accufuser® WooYoung Medical, Seoul,Korea) with analgesics containing morphine (40 mg), ketorolac (180 mg), andramo-setron (0.6 mg) in normal saline and in a total volume of 100 ml. . This device was set to deliver a basal infusion of 2 ml/h, andbolus doses of 0.5 ml with a 15 min lockout time.. Duration post op. Concurrent medication/care: The induction of anesthesia was commenced with a slow (30-60 s) i.v. bolus dose of remifentanil (1 μg/kg), followed by propofol (1-2 mg/kg), and tracheal intubation was facilitated with rocuronium (0.9 mg/kg) in all groups. As mentioned above, the infusion of remifentanil was fixed in all groups, and anesthesia was maintained with desflurane at an initial end-tidal concentration of 1 minimum alveolar concentration (MAC) and oxygen-medical air mixture (fraction of oxygen, 50%). During surgery, anesthesia levels were monitored by stepwise titration of the desflurane concentration by 1 vol%, based on hemodynamic changes and targeting a bispectral index (BIS) from 40-60. Our criterion for hemodynamic change was a systolic blood pressure that exceeded values between ± 20% of pre-induction values. Patients received 10 mg i.v. bolus doses of ephedrine in cases of persistent hypotension. If heart rate decreased to less than 50 beats/min, a 0.5 mg i.v. atropine bolus was administered intrave-nously. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain VAS 1 hour post op at 1 hour post op; Group 1: mean 53.6 (SD 12.4); n=25, Group 2: mean 59.05 (SD 16.78); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain Tactile pain threshhold 24 hours post op at 24 hours post op; Reported in the graph only
Ketamine group ~120; Group L~120; Group H ~75;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: Cumulative PCA (morphine + ketorolac) volume containing morphine 24 hours at 24 hours; Group 1: mean 58.1 ml (SD 1.9); n=25, Group 2: mean 59.3 ml (SD 2.737); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (< 6 hours post op) - Actual outcome: Ketorolac consumption during 1 hour post op at 1 hour post op; Group 1: mean 25.2 mg (SD 7.1); n=25, Group 2: mean 26.4 mg (SD 6.54); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Nielsen 2017[919]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Denmark; Setting: n/a
Line of therapy	Not applicable
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients undergoing lumbar fusion surgery during general anesthesia were approached for inclusion in the trial. Additional inclusion criteria were chronic back pain >3 months preoperatively, daily use of strong opioids for back pain>6 weeks preoperatively (morphine oxycodone, tramadol, buprenorphine, fentanyl or ketobemidone), age 18 to 85 years, ASA of 1 to 3, and body mass index 18 to 40 kg/m²
Exclusion criteria	Inability to cooperate, inability to speak or understand Danish, participation in other drug trials, daily use of methadone, current or previous psychotic episodes, uncontrolled hypertension, increased intraocular pressure, pregnancy, allergy to drugs applied in the trial, and alcohol or drug abuse
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine- 57(14); CTRL - 55(13). Gender (M:F): 98/49. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2 and 3). 3. Type of surgery: ortho/large joint replacement (lumbar fusion).
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine group - S-ketamine (0.25 mg/mL) bolus 0.5 mg/kg, followed by infusion S-ketamine 0.25 mg kg-1 h-1. Forty five minutes before expected completion of the surgery, morphine 0.4 mg kg was administered intravenously. For all patients, post operative pain treatment during the first 24 hours consisted of 1000 mg oral paracetamol every 6 hours, starting 2 hours postoperatively, and the patients usual opioid treatment. In addition all patients received IV PCA with morphine (bolus 2.5 mg, lockout time 5 minutes, and no background infusion) Rescue medication (IV morphine 2.5 mg p.n.) was administered by nurse in PACU for the first postoperative hour in case the PCA was insufficient.. Duration 24 ours post op. Concurrent medication/care: One hour before the surgery, all patients received their usual dose of opioids and oral paracetamol 1000 mg. general anesthesia was induced and maintained with propofol(variable rate) and remifentanil (fixed rate 40 µg kg-1 h-1). Rocuronium (0.6-1.0) mg/kg) was used to facilitate orotracheal intubation with a cuffed tube.. Indirectness:

	No indirectness (n=75) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group - placebo(isotonic saline) bolus, followed by infusion S-ketamine 0.25 mg kg-1 h-1. Forty five minutes before expected completion of the surgery, morphine 0.4 mg kg was administered intravenously. For all patients, post operative pain treatment during the first 24 hours consisted of 1000 mg oral paracetamol every 6 hours, starting 2 hours postoperatively, and the patients usual opioid treatment. In addition all patients received IV PCA with morphine (bolus 2.5 mg, lockout time 5 minutes, and no background infusion) Rescue medication (IV morphine 2.5 mg p.n.) was administered by nurse in PACU for the first postoperative hour in case the PCA was insufficient.. Duration 24 hours post op. Concurrent medication/care: One hour before the surgery, all patients received their usual dose of opioids and oral paracetamol 1000 mg. general anesthesia was induced and maintained with propofol(variable rate) and remifentanil (fixed rate 40 µg kg-1 h-1). Rocuronium (0.6-1.0) mg/kg) was used to facilitate orotracheal intubation with a cuffed tube.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 6 hours at 6 hours; Reported in the graph only (no SD)
Ketamine group-46; Control - 48;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1
- Actual outcome: Pain VAS at 24 hours at 24 hours; Reported in the graph only (no SD)
Ketamine group-44; Control - 44;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: PCA morphine consumption at 24 hours; Group 1: mean 79 mg (SD 47); n=73, Group 2: mean 121 mg (SD 53); n=74
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1
- Actual outcome: Rescue morphine consumption at 24 hours; Median(quartiles)
Ketamine group - 13(3-26); control 15(7-26);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea at 24 hours; Group 1: 13/73, Group 2: 17/74 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 - Actual outcome: Vomiting (episodes) at 24 hours; Group 1: 49/73, Group 2: 68/74 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 - Actual outcome: Vomiting (number of people) at 24 hours; Group 1: 22/73, Group 2: 21/74 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Li 2016[608]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in China; Setting: post-anesthesia care unit
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	scheduled to undergo abdominal surgery (hemicolectomy, exploratory laparotomy, extended radical cystectomy and anephrectomy, and abdominal aortic aneurysm surgery), who were between the ages of 18 to 70 years, and who were in good health or with mild systemic diseases according to the American Society of Anesthesiologists (ASA, grade 1 or 2) were recruited.
Exclusion criteria	Define

Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): saline group - 48.94(9.42); Ketamine 53.1(10.56). Gender (M:F): Define. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (hemicolectomy, exploratory laparotomy, extended radical cystectomy and nephrectomy, and abdominal aortic aneurysm surgery).
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Post-operative pain was controlled by titration of IV morphine by nurses who were blinded to the grouping. The patients were administered morphine (3 mg/kg with a lockout time of 20 min until 1 h-programmed via IV-PCA infusion pump as post-operative analgesia in the recovery room. Ketamine group infused intravenously with 3 mg/kg/h ketamine (ketamine group; n = 17). Duration 24 hours. Concurrent medication/care: General anesthesia was induced with 3.0 mg/kg fentanyl, 5 mg/kg thiopental sodium, and 1.5 mg/kg succinylcholine. Atracurium was maintained with isoflurane in 50 % nitrous oxide and 0.3 – 1.3 μg/kg/min sufentanil [8]. Neuromuscular relaxation was antagonized at skin closure, and patients were tracheally extubated before transfer to the recovery room. After surgery, patients were given supplemental oxygen at 5 L/min via a facemask. After arrival in the recovery room, residual neuromuscular blockade was reversed with neostigmine (40 μg/kg) and atropine (15 μg/kg). Indirectness: No indirectness (n=15) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Post-operative pain was controlled by titration of IV morphine by nurses who were blinded to the grouping. The patients were administered morphine (3 mg/kg with a lockout time of 20 min until 1 h-programmed via IV-PCA infusion pump as post-operative analgesia in the recovery room. Control group infused intravenously with isotonic saline. Duration 24 hours. Concurrent medication/care: General anesthesia was induced with 3.0 mg/kg fentanyl, 5 mg/kg thiopental sodium, and 1.5 mg/kg succinylcholine. Atracurium was maintained with isoflurane in 50 % nitrous oxide and 0.3 – 1.3 μg/kg/min sufentanil [8]. Neuromuscular relaxation was antagonized at skin closure, and patients were tracheally extubated before transfer to the recovery room. After surgery, patients were given supplemental oxygen at 5 L/min via a facemask. After arrival in the recovery room, residual neuromuscular blockade was reversed with neostigmine (40 μg/kg) and atropine (15 μg/kg). Indirectness: No indirectness
Funding	Academic or government funding (The authors thank Qilu Hospital of Shandong University for funding this project (no. QHSU-235).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

	Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain (VAS) 12 hours post op at 12 hours; reported in the graph only at 6 hours: Ketamine group~ 32 Saline Group~43 at 24 hours: Ketamine group~25 Saline Group~32; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pain (VRS) 12 hours post op at 12 hours; Mean; , Comments: reported in the graph only at 6 hours: Ketamine group~ 3 Saline Group~3.3 at 24 hours: Ketamine group~2 Saline Group~2.2; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: mean cumulative morphine consumption during 24 hours at 24 hours; Group 1: mean 25.13 mg (SD 2.9); n=17, Group 2: mean 33.4 mg (SD 2.5); n=15 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: PONV (Nausea+vomiting) at 24 hours; Group 1: 1/17, Group 2: 6/15 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Sveticic 2008[1222]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=352)
Countries and setting	Conducted in Switzerland; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention + follow up:

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	After obtaining approval from the ethics committee of the University of Bern, Switzerland, patients undergoing major elective orthopedic surgery (Table 1) were studied. Written informed consent was obtained from all patients.
Exclusion criteria	Exclusion criteria were any contraindication to ketamine or morphine, age □18 yr, intake of psychotropic drugs, daily intake of opioids for a period □1 wk, and lack of patient's cooperation.
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): Morphine+ketamine group - 48 (17.2); Morphine 47.3(17.2. Gender (M:F): morphine ketamine - 87/89; morphine group 93/83. Ethnicity:
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable 3. Type of surgery: ortho/large joint replacement (elective orthopedic surgery).
Indirectness of population	No indirectness
Interventions	(n=176) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. After major elective orthopedic surgery, patients received a bolus of morphine plus ketamine 1.5 mg each (Group MK, n _176) . Duration post op. Concurrent medication/care: Either general or regional anesthesia was performed,as decided by the anesthesiologist in charge of the patient. Patients were premedicated orally with midazolam 7.5 mg, 20–30 min before anesthesia. They were monitored with electrocardiogram, noninvasive arterial blood pressure (one measurement every 5 min), and oxygen saturation using pulse oximetry. General anesthesia was induced with IV fentanyl 0.15– 0.2 mg; thiopental 5–7 mg/kg or propofol 2–2.5 mg/kg or etomidate 0.2– 0.3 mg/kg; vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg. After tracheal intubation, a mixture of oxygen (30% inspired concentration) with nitrous oxide was administered,supplemented by either isoflurane (0.3– 0.5 vol% end-tidal concentration) or propofol (2–4 _g/mL target-controlled infusion). If there were signs of inadequate analgesia, IV boluses of 0.05– 0.2 mg fentanyl and 1.0 –2.0 mg vecuronium or atracurium 10–20 mg were administered at the discretion of the attending anesthesiologist. At the end of surgery, residual neuromuscular blockade was reversed with 2.5 mg neostigmine and 0.5 mg glycopyrrolate.Regional anesthesia was performed as a single-shot injection of a maximum 50 mL of mepivacaine 1% with sodium bicarbonate or ropivacaine 0.75% for peripheral nerve blockade and 12.5–17.5 mg bupivacaine 0.5% for spinal anesthesia.

	Either general or regional anesthesia was performed,as decided by the anesthesiologist in charge of the patient. Patients were premedicated orally with midazolam 7.5 mg, 20–30 min before anesthesia. They were monitored with electrocardiogram, noninvasive arterial blood pressure (one measurement every 5 min), and oxygen saturation using pulse oximetry. General anesthesia was induced with IV fentanyl 0.15– 0.2 mg; thiopental 5–7 mg/kg or propofol 2–2.5 mg/kg or etomidate 0.2– 0.3 mg/kg; vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg. After tracheal intubation, a mixture of oxygen (30% inspired concentration) with nitrous oxide was administered,supplemented by either isoflurane (0.3– 0.5 vol% end-tidal concentration) or propofol (2–4 _g/mL target-controlled infusion). If there were signs of inadequate analgesia, IV boluses of 0.05– 0.2 mg fentanyl and 1.0 –2.0 mg vecuronium or atracurium 10–20 mg were administered at the discretion of the attending anesthesiologist. At the end of surgery, residual neuromuscular blockade was reversed with 2.5 mg neostigmine and 0.5 mg glycopyrrolate.Regional anesthesia was performed as a single-shot injection of a maximum 50 mL of mepivacaine 1% with sodium bicarbonate or ropivacaine 0.75% for peripheral nerve blockade and 12.5–17.5 mg bupivacaine 0.5% for spinal anesthesia. . Indirectness: No indirectness (n=176) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. After major elective orthopedic surgery, patients received either PCA with morphine bolus 1.5 mg (Group M, n _176) . Duration post op. Concurrent medication/care: Either general or regional anesthesia was performed,as decided by the anesthesiologist in charge of the patient. Patients were premedicated orally with midazolam 7.5 mg, 20–30 min before anesthesia. They were monitored with electrocardiogram, noninvasive arterial blood pressure (one measurement every 5 min), and oxygen saturation using pulse oximetry. General anesthesia was induced with IV fentanyl 0.15– 0.2 mg; thiopental 5–7 mg/kg or propofol 2–2.5 mg/kg or etomidate 0.2– 0.3 mg/kg; vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg. After tracheal intubation, a mixture of oxygen (30% inspired concentration) with nitrous oxide was administered,supplemented by either isoflurane (0.3– 0.5 vol% end-tidal concentration) or propofol (2–4 _g/mL target-controlled infusion). If there were signs of inadequate analgesia, IV boluses of 0.05– 0.2 mg fentanyl and 1.0 –2.0 mg vecuronium or atracurium 10–20 mg were administered at the discretion of the attending anesthesiologist. At the end of surgery, residual neuromuscular blockade was reversed with 2.5 mg neostigmine and 0.5 mg glycopyrrolate.Regional anesthesia was performed as a single-shot injection of a maximum 50 mL of mepivacaine 1% with sodium bicarbonate or ropivacaine 0.75% for peripheral nerve blockade and 12.5–17.5 mg bupivacaine 0.5% for spinal anesthesia. Either general or regional anesthesia was performed,as decided by the anesthesiologist in charge of the patient.

	Patients were premedicated orally with midazolam 7.5 mg, 20–30 min before anesthesia. They were monitored with electrocardiogram, noninvasive arterial blood pressure (one measurement every 5 min), and oxygen saturation using pulse oximetry. General anesthesia was induced with IV fentanyl 0.15– 0.2 mg; thiopental 5–7 mg/kg or propofol 2–2.5 mg/kg or etomidate 0.2– 0.3 mg/kg; vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg. After tracheal intubation, a mixture of oxygen (30% inspired concentration) with nitrous oxide was administered,supplemented by either isoflurane (0.3– 0.5 vol% end-tidal concentration) or propofol (2–4 _g/mL target-controlled infusion). If there were signs of inadequate analgesia, IV boluses of 0.05– 0.2 mg fentanyl and 1.0 –2.0 mg vecuronium or atracurium 10–20 mg were administered at the discretion of the attending anesthesiologist. At the end of surgery, residual neuromuscular blockade was reversed with 2.5 mg neostigmine and 0.5 mg glycopyrrolate.Regional anesthesia was performed as a single-shot injection of a maximum 50 mL of mepivacaine 1% with sodium bicarbonate or ropivacaine 0.75% for peripheral nerve blockade and 12.5–17.5 mg bupivacaine 0.5% for spinal anesthesia. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain Vrs(at rest) at post op; Group 1: mean 0.77 (SD 0.56); n=176, Group 2: mean 0.77 (SD 0.42); n=176
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Additional Ketorolac at post op; Group 1: 24/176, Group 2: 12/176
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Additional metamizole at post op; Group 1: 15/176, Group 2: 12/176
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: respiratory depression+nausea at post op; Group 1: 128/176, Group 2: 113/176
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Katz 2004[496]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=143)
Countries and setting	Conducted in Canada; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 72 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for radical prostatectomy for prostate cancer. American Society of Anesthesiologists physical status I-II, age between 19 and 75 years.
Exclusion criteria	contraindications to (iv) patient-controlled analgesia (PCA) with morphine, American Society of Anesthesiologists physical status)II, history of major psychiatric disorder, and chronic opioid use.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 62 (6). Gender (M:F): Not reported. Ethnicity: NA
Further population details	1. Age: >60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 3. Type of surgery: lower and upper GI
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Pre-incision i.v. ketamine bolus dose (0.2 ml kg-t) and an i.v. infusion (0.0025 rnl kg-1 min-1). Post-incision saline. All patients received i.v. fentanyl (1 ug kg-1, 25 ug ml-1) every 80 min starting approximately 5 min before induction of general anesthesia. After induction of general anesthesia, all patients received a bolus dose of i.v. fentanyl (0.5 ug kg-'). This was followed immediately by an i.v. bolus dose (0.2 ml kg-') and an i.v. infusion (0.0025 ml kg-t min-t) from the first syringe labeled 'pre-incision'. Seventy minutes after incision, the first infusion was stopped and all patients received a bolus dose of i.v. fentanyl (0.5 pg tg-r;. ttris was followed immediately by an i.v. bolus dose (0.2 ml kg-r) and an i.v. infusion (0.0025 ml kg-t min-l; from the second syringe

	labeled 'post-incision'. The second infusion was stopped after 80 min, approximately 150 min after incision.. Duration n/a. Concurrent medication/care: Patients received midazolam l-2mg i.v. as premedication approximately t h before surgery. General anesthesia was induced with thiopental 4-6mgkg-r. Intubation followed the administration of d-tubo curarine (3.0-4.5 mg) and succinylcholine 1.0-1.5 mg kg-r. General anesthesia was maintained with 60Vo N2O in 02 and isoflurane.. Indirectness: No indirectness (n=50) Intervention 2: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Pre-incision saline. Post-incision i.v. ketamine bolus dose (0.2 ml kg-t) and an i.v. infusion (0.0025 rnl kg-1 min-1). All patients received i.v. fentanyl (1 ug kg-1, 25 ug ml-1) every 80 min starting approximately 5 min before induction of general anesthesia. After induction of general anesthesia, all patients received a bolus dose of i.v. fentanyl (0.5 ug kg-'). This was followed immediately by an i.v. bolus dose (0.2 ml kg-') and an i.v. infusion (0.0025 ml kg-t min-t) from the first syringe labeled 'pre-incision'. Seventy minutes after incision, the first infusion was stopped and all patients received a bolus dose of i.v. fentanyl (0.5 pg tg-r;. ttris was followed immediately by an i.v. bolus dose (0.2 ml kg-r) and an i.v. infusion (0.0025 ml kg-t min-l; from the second syringe labeled 'post-incision'. The second infusion was stopped after 80 min, approximately 150 min after incision.. Duration n/a. Concurrent medication/care: Patients received midazolam l-2mg i.v. as premedication approximately t h before surgery. General anesthesia was induced with thiopental 4-6mgkg-r. Intubation followed the administration of d-tubo curarine (3.0-4.5 mg) and succinylcholine 1.0-1.5 mg kg-r. General anesthesia was maintained with 60Vo N2O in 02 and isoflurane.. Indirectness: No indirectness (n=46) Intervention 3: Opioid (IV) and placebo - Opioid + placebo. Pre-incision saline. Post-incision saline. All patients received i.v. fentanyl (1 ug kg-1, 25 ug ml-1) every 80 min starting approximately 5 min before induction of general anesthesia. After induction of general anesthesia, all patients received a bolus dose of i.v. fentanyl (0.5 ug kg-'). This was followed immediately by an i.v. bolus dose (0.2 ml kg-') and an i.v. infusion (0.0025 ml kg-t min-t) from the first syringe labeled 'pre-incision'. Seventy minutes after incision, the first infusion was stopped and all patients received a bolus dose of i.v. fentanyl (0.5 pg tg-r;. ttris was followed immediately by an i.v. bolus dose (0.2 ml kg-r) and an i.v. infusion (0.0025 ml kg-t min-l; from the second syringe labeled 'post-incision'. The second infusion was stopped after 80 min, approximately 150 min after incision.. Duration n/a. Concurrent medication/care: Patients received midazolam l-2mg i.v. as premedication approximately t h before surgery. General anesthesia was induced with thiopental 4-6mgkg-r. Intubation followed the administration of d-tubo curarine (3.0-4.5 mg) and succinylcholine 1.0-1.5 mg kg-r. General anesthesia was maintained with 60Vo N2O in 02 and isoflurane.. Indirectness: No indirectness
Funding	Academic or government funding (Canadian Institutes of Health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE (PRE-OP) + OPIOID versus OPIOID + PLACEBO	

Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain (VAS) at 6 hours; Mean; (p: >0.05), Comments: There were no significant differences among the groups in VAS pain scores); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: Pain (VAS) at 6-24 hours; Mean; (p: >0.05), Comments: There were no significant differences among the groups in VAS pain scores); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (< 6 hours post op) - Actual outcome: PCA morphine consumption at 0-6 hours; Group 1: mean 20.2 mg (SD 7.9); n=47, Group 2: mean 20.9 mg (SD 7.6); n=46 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: PCA morphine consumption at 6-24 hours; Group 1: mean 28 mg (SD 10.7); n=47, Group 2: mean 31.4 mg (SD 13.5); n=46 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE (POST-OP) + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Amount of additional medication use (< 6 hours post op) - Actual outcome: PCA morphine consumption at 0-6 hours; Group 1: mean 22.1 mg (SD 8.3); n=50, Group 2: mean 20.9 mg (SD 7.6); n=46; Comments: means on 0-3 hours and 3-6 hours combined. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: PCA morphine consumption at 6-24 hours; Group 1: mean 33.2 mg (SD 14); n=50, Group 2: mean 31.4 mg (SD 13.5); n=46 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Nesher 2008[905]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Israel; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	60 patients scheduled for elective MIDCAB or OPCAB or for lung resection via anterolateral thoracotomy were enrolled.
Exclusion criteria	ASA physical class>3, emergency surgery, concommitant valvular surgery, Q-wave mycardial infarct occuring during the previous 3 weeks or poor ventricular function. Body mass index >35kg/m², past or current neuropathy or psycological disturbances, the use of centrally active psychomimetic drugs, chronic liver failure requiring dialysis, allergy to ketamine, morphine or NSAIDS, evidence of sepsis or infection up to 1 week prior to randomization.,
Recruitment/selection of patients	sequential
Age, gender and ethnicity	Age - Mean (SD): Ketamine 60(15) control 59(16). Gender (M:F): 18/42. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2,3). 3. Type of surgery: Not applicable (Thoracotomy for MIDCAB, lung tumor resection or median sternotomy for OPCAB).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA drug bolus injections consisted of 1mg morphine + 5 mg ketamine. the device was preset to deliver bolus whenever patient activated it, controlled by 7 min lockout period. if pain was not atenuated within 30 min of initial activation, a rescue dose of im diclofenac was available.. Duration 72 h. Concurrent medication/care: Standardized anesthesia consisted of midazolam 2mg, propofol 1 mg/kg, fentanyl 5-20 µg/kg and pancuronium 0.1 mg/kg to facilitate endotracheal intubation.. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA drug bolus injections consisted of 1.5 mg morphine alone. the device was preset to deliver bolus whenever patient activated it, controlled by 7 min lockout period. if pain was not atenuated within 30 min of initial activation, a rescue dose of im diclofenac was available.. Duration 72 h. Concurrent medication/care: Standardized anesthesia consisted of midazolam 2mg, propofol 1 mg/kg, fentanyl 5-20 µg/kg and pancuronium 0.1 mg/kg to facilitate endotracheal intubation. Indirectness: No indirectness

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 6 h at 6 h; Reported in the graph only
ketamine~4; control~4.5;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1
- Actual outcome: Pain VAS at 24 h at 24 h; Reported in the graph only
ketamine~3; control~3.2;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: mean morphine consumption 24 h at 24 h; Group 1: mean 1 mg (SD 1.4); n=28, Group 2: mean 2 mg (SD 2.3); n=29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1
- Actual outcome: diclofenac request at 24 h; Group 1: 10/28, Group 2: 17/29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: PONV at 24 h; Group 1: 11/28, Group 2: 17/29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Kollender 2008[541]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	(n=57)
Countries and setting	Conducted in Israel; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 96 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA 1-3 patients scheduled for one or two major bone and soft tissue tumour surgeries.
Exclusion criteria	Pre-operative pain of >4/10 on VAS scale. Allergy to study drugs.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 42 (16). Gender (M:F): 24/53. Ethnicity: NA
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA1-3). 3. Type of surgery: ortho/large joint replacement
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PACU attending physician started IV PCA device in all patients when sufficiently awake. Analgesia started when pain score reached ≥5. Solution consisted 1mg morphine, 5 mg ketamine with 7 minute lockout. . Duration 96 hours. Concurrent medication/care: Standardised balanced general anaesthesia. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PACU attending physician started IV PCA device in all patients when sufficiently awake. Analgesia started when pain score reached ≥5. Solution consisted 1.5mg morphine with 7 minute lockout. . Duration 96 hours. Concurrent medication/care: Standardised balanced general anaesthesia. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: VAS: Pain at 96 hours; p: <0.001, Comments: Pain was lower over 10 with opioid + ketamine compared to opioid only (values presented in graph format));
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: morphine use at 24 hours; Group 1: mean 14.6 mg/patient (SD 11.4); n=28, Group 2: mean 32.9 mg/patient (SD 24.9); n=29; Comments: Groups received different dose of morphine as standard Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: PONV at 3 days; Group 1: 6/28, Group 2: 12/29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 Protocol outcome 4: Functional measures - Actual outcome: Physical therapist score at 96 hours; Group 1: mean 8.8 (SD 1.4); n=14, Group 2: mean 6.4 (SD 1.4); n=14 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Kwok 2004[562]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=135)
Countries and setting	Conducted in Hong Kong (China); Setting: Not reported
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	women, ASA physical status I or II, aged between 18 and 65 yr, scheduled for laparoscopic gynecologic surgery

Exclusion criteria	history of psychiatric disorder, chronic pain syndrome, or drug and alcohol abuse. Patients receiving regular opioids or drugs with known analgesic properties in the 24 h before surgery.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 34 (6). Gender (M:F): All women. Ethnicity: Not reported
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 3. Type of surgery: gynae-oncology
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. IV ketamine 0.15 mg/kg (made up to 10 mL with normal saline) immediately before the induction of anesthesia followed by normal saline 10mLafter wound closure. Post-operatively analgesia was initially provided with IV morphine 1.5 mg and was repeated every 5min until the patient was comfortable or when the visual analog scale (VAS) pain score was <20 mm. On the ward, patients received IM morphine 0.15 mg/kg every 4h.. Duration n/a. Concurrent medication/care: Anesthesia was induced with propofol 2 mg/kg g/kg IV. Atracurium 0.5 mg/kg was and fentanyl 2 administered to facilitate tracheal intubation. Anesthesia was then maintained with nitrous oxide 70% and isoflurane 0.5%–1.0% in oxygen. The lungs were mechanically ventilated, and the end-tidal carbon dioxide concentration was maintained between 5.0%–5.5%. At the end of surgery, anesthesia was discontinued, and residual neuromuscular blockade was antagonized by neostigmine 40g/kg and atropine 20 g/kg. The trachea was extubated when the patient became fully awake. Anesthetic time was defined from the start of induction to the time when nitrous oxide was discontinued, whereas the duration from skin incision to the last suture was designated as surgical time.. Indirectness: No indirectness (n=45) Intervention 2: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Saline before the induction of anesthesia and ketamine 0.15 mg/kg after wound closure. Post-operatively analgesia was initially provided with IV morphine 1.5 mg and was repeated every 5min until the patient was comfortable or when the visual analog scale (VAS) pain score was <20 mm. On the ward, patients received IM morphine 0.15 mg/kg every 4h.. Duration n/a. Concurrent medication/care: Anesthesia was induced with propofol 2 mg/kg g/kg IV. Atracurium 0.5 mg/kg was and fentanyl 2 administered to facilitate tracheal intubation. Anesthesia was then maintained with nitrous oxide 70% and isoflurane 0.5%–1.0% in oxygen. The lungs were mechanically ventilated, and the end-tidal carbon dioxide concentration was maintained between 5.0%–5.5%. At the end of surgery, anesthesia was discontinued, and residual neuromuscular blockade was antagonized by neostigmine 40g/kg and atropine 20 g/kg. The trachea was extubated when the patient became fully awake. Anesthetic time was defined from the start of induction to the time when nitrous oxide was discontinued, whereas the duration from skin incision to the last suture was designated as surgical time.. Indirectness: No indirectness (n=45) Intervention 3: Opioid (IV) and placebo - Opioid + placebo. Normal saline before the induction of anesthesia and after wound closure. Post-operatively analgesia was initially provided with IV morphine 1.5

	mg and was repeated every 5min until the patient was comfortable or when the visual analog scale (VAS) pain score was <20 mm. On the ward, patients received IM morphine 0.15 mg/kg every 4h.. Duration n/a. Concurrent medication/care: Anesthesia was induced with propofol 2 mg/kg g/kg IV. Atracurium 0.5 mg/kg was and fentanyl 2 administered to facilitate tracheal intubation. Anesthesia was then maintained with nitrous oxide 70% and isoflurane 0.5%–1.0% in oxygen. The lungs were mechanically ventilated, and the end-tidal carbon dioxide concentration was maintained between 5.0%–5.5%. At the end of surgery, anesthesia was discontinued, and residual neuromuscular blockade was antagonized by neostigmine 40g/kg and atropine 20 g/kg. The trachea was extubated when the patient became fully awake. Anesthetic time was defined from the start of induction to the time when nitrous oxide was discontinued, whereas the duration from skin incision to the last suture was designated as surgical time.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE (PRE-OP) + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain (VAS) at 6 hours; Mean; , Comments: During the first 6 h after surgery, the pain scores were significantly lower in patients receiving ketamine before the induction of anesthesia compared with those in the placebo groups (P<0.001).;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain (VAS) at 24 hours; Mean; , Comments: pain scored after 6 hours were low and were not significantly different between groups. ;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: total morphine (mg) at unclear; Group 1: mean 1.5 mg (SD 2); n=45, Group 2: mean 3.4 mg (SD 2.7); n=45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Length of hospital stay
- Actual outcome: hospital discharge (day) at n/a; Group 1: mean 2.8 days (SD 0.8); n=45, Group 2: mean 3 days (SD 0.8); n=45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE (POST-OP) + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain (VAS) at 6 hours; Mean; , Comments: During the first 6 h after surgery, the pain scores were not significantly lower in patients

receiving ketamine after the induction of anesthesia compared with those in the placebo groups (P>0.05).; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: total morphine (mg) at unclear; Group 1: mean 2.9 (SD 3.1); n=45, Group 2: mean 3.4 (SD 2.7); n=45 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: hospital discharge (day) at n/a; Group 1: mean 2.9 days (SD 0.5); n=45, Group 2: mean 3 days (SD 0.8); n=45 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Lee 2014[592]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in South Korea; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 1 hour
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients aged 20-70 years and of American Society of Anesthesiologists physical status 1 or 2 scheduled for laparoscopic cholecystectomy under general anesthesia
Exclusion criteria	Patients with hepatic diseases, renal diseases, diabetes mellitus or cardiac diseases, recent administration of opioids or beta blockers, asthma, air way hypersensitivity, diseases related to the airway, or allergies to

	drugs
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 44 (11.8). Gender (M:F): 16/24. Ethnicity: NA
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 3. Type of surgery: lower and upper GI
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Anesthesia induction was performed with propofol (1.5 mg/kg), and effect-site target concentration of remifentanil 4 ng/ml (target-controlled infusion, 4 ng/ml) was infused. Ketamine (0.3 mg/kg) was IV injected during anesthesia induction, and 3 µg/kg/min was continuously infused during surgery.. Duration n/a. Concurrent medication/care: Midazolam 2 mg and glycopyrrolate 0.2 mg were injected intramuscularly as premedication.. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Anesthesia induction was performed with propofol (1.5 mg/kg), and effect-site target concentration of remifentanil 4 ng/ml (target-controlled infusion, 4 ng/ml) was infused. Saline was IV injected during anesthesia induction, and was continuously infused during surgery.. Duration n/a. Concurrent medication/care: Midazolam 2 mg and glycopyrrolate 0.2 mg were injected intramuscularly as premedication.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score (VAS) at 0-1 hours post-op; Mean; , Comments: Mean pain scores were significantly lower with ketamine at 0, 5 and 15 minutes post operatively (p<0.05). Pain at 30, 45 and 60 minutes was not significantly different between the ketamine and saline groups.
Values presented as a graph.;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Total fentanyl consumption (ug) at 0-1 hours post-op; Group 1: mean 39 ug (SD 38); n=20, Group 2: mean 67.5 ug (SD 37.5); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ;

study	Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Lenzmeier 2008[599]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=22)
Countries and setting	Conducted in USA; Setting: Military Medical facility, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	not specified
Exclusion criteria	not specified
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): Ketamine: 29.72 ± 8.5; Placebo: 31.63 ± 6.68. Gender (M:F): all female . Ethnicity: NA
Further population details	1. Age: <60 years (Ketamine: 29.72 ± 8.5; Placebo: 31.63 ± 6.68). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (laparoscopic abdominal procedures).
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. 0.5mg/kg dose of ketamine by IV bolus with induction of general anesthesia. . Duration preoperatively. Concurrent medication/care: Opioids given as rescue medication but not specified which opioid or regimen. (n=11) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. 0.5mg/kg dose of placebo by IV bolus with induction of general anesthesia. . Duration preoperatively. Concurrent medication/care: Opioids given as rescue medication but not specified which opioid or regimen. . Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Amount of additional medication use (< 6 hours post op) - Actual outcome: No. Patients needing additional analgesic medication in PACU at ≤6 hours postoperatively; Group 1: 9/11, Group 2: 11/11 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Morphine consumption in PACU at ≤6 hours postoperatively; Median : Ketamine: 3.8mg; Opioid: 6.0mg milligrams); Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: VAS score on admission to PACU at ≤6 hours postoperatively; Median : Ketamine: 24; Opioid: 66 pain score visual analogue scale 0-100 Top=High is poor outcome; Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Darwish 2005[220]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Estonia; Setting: n/a
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	60 adult patients who were scheduled to open colorectal surgery lasting at least 3 hours. all patients were ASA 1-3
Exclusion criteria	Patients were excluded from the study when: a. immediate extubation was not planned after surgery; b. they

	had chronic inflammatory disease including inflammatory bowel disease c. they regularly took analgesics or had used opioids within 12 h of surgery. d. they had history of drug or alcohol abuse, psychiatric disorder, or obesity (>130% of ideal body weight) e. there were contraindications to the selfadministration of opioids (unable to understand PCA) or if sedation score was more than 1.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine 63(8); control 60(11). Gender (M:F): 31/29. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2 and 3). 3. Type of surgery: lower and upper GI (abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine diluted to 2.5 mg/ml in isotonic sodium chloride. a continuous iv infusion of the study drug was started 1 min after thiopental injection. The initial bolus of ketamine was 0.15 mg/kg and was followed by a maintenance infusion of 2µg/kg/min until skin closure. 30 min before end of surgery 0.15 mg/kg bolus dose of morphine was administered iv. During the postoperative period 3 mg of morphine was given iv at 5 min intervals until behavioral pain score was<1 In PACU PCA morphine 1 mg as an iv bolus lockout interval 15 min. Duration 24 hours. Concurrent medication/care: Anesthesia was induced with thiopentone 6mg/kg followed by vecuronium 01 mg/kg to facilitate orotracheal intubation. 2 min after thiopentone injection 1µg/kg initial dose of remifentanil was given over 6o seconds. After tracheal intubation, the patients were ventilated to normocapnia using 50% oxygen without nitrous oxide. anesthesia was maintained with sevoflurane. Remifentanil was infused throughout surgery in all patients; the infusion was started at 0.15 µg/kg/min and subsequently increases stepwise by 0.05 0.15 µg/kg/min. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Isotonic sodium chloride. a continuous iv infusion of the study drug was started 1 min after thiopental injection. 30 min before end of surgery 0.15 mg/kg bolus dose of morphine was administered iv. During the postoperative period 3 mg of morphine was given iv at 5 min intervals until behavioral pain score was<1 In PACU PCA morphine 1 mg as an iv bolus lockout interval 15 min. Duration 24 hours. Concurrent medication/care: Anesthesia was induced with thiopentone 6mg/kg followed by vecuronium 01 mg/kg to facilitate orotracheal intubation. 2 min after thiopentone injection 1µg/kg initial dose of remifentanil was given over 60 seconds. After tracheal intubation, the patients were ventilated to normocapnia using 50% oxygen without nitrous oxide. anesthesia was maintained with sevoflurane. Remifentanil was infused throughout surgery in all patients; the infusion was started at 0.15 µg/kg/min and subsequently increases stepwise by 0.05 0.15 µg/kg/min. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS 4h at post op 4h; reported in the graph
Ketamine group~37; control ~55;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VAS 24h at post op 24h; Mean; , Comments: Reported in the graph
Ketamine~36, control~44;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Cumulative post op Morphine consumption (mg) at 4 h at 4 h; Median (range)
Ketamine - 16 (9-22); Control - 21 (15-29);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Cumulative post op Morphine consumption (mg) at 24 h at 24 h; Median (range)
Ketamine - 21 (13-30); Control - 38 (20-48);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Morphine given in PACU (mg) at 24 h; Group 1: mean 9.2 mg (SD 1.1); n=30, Group 2: mean 12 mg (SD 0.8); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea+vomiting at post op; Group 1: 4/30, Group 2: 6/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Bauchat 2011[85]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=188)
Countries and setting	Conducted in USA; Setting: Conducted in Prentice Wmens hospital.
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Women aged ≥37 weeks of gestation, ASA physical status 1-2, scheduled for elective cesarean delivery whose anesthetic plan included spinal anesthesia with intrathecal morphine and i.v.ketorolac for postoperative analgesia
Exclusion criteria	women were excluded if their body mass index was ≥40 kg/m² or if they had allergies to any of the study medications, contraindications to spinal anesthesia, or history of haliucinations, substance abuse, chronic opioid therapy or chronic pain.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (range): Ket - 34(31-37); CTRL-34(31-37). Gender (M:F): All female. Ethnicity: African american (ketamine -4;CTRL-6); Asian american (Ket-4; CTRL-1); Caucasian (Ket-67; CTRL-68); Hispanic (Ket-4; CTRL-8); Other (Ket-6; CTRL-6)
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (Cesarean section).
Indirectness of population	No indirectness
Interventions	(n=94) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine group - received Ketamine 10 mg diluted to 20mL with 0.9% saline. In Pacu patients received i.v. ketorolac 30 mg every 6 h to 24 hours the first dose given in PACU, bu were allowed to refuse these schedulled analgesia if they experienced discomfort. Rescue medication consisted of 1 tablet of acetaminophen/hydrocodone was provided after 1 hour if the pain was not relieved to the subjects satisfaction. Between 24-72 hours analgesia was provided at the patients request with ibuprofen 600 mg every 6 h and 1-2 tablets of cetaminphen 325 mg/hydrocodone 10 mg every 4 h.. Duration 72 hours. Concurrent medication/care: All patients received intrathecal hyperbaric bupivacaine 12 mg, fentanyl 15µg and morphine 150 µg as a single injection. Indirectness: No indirectness

	(n=94) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group - received 20 mL 0.9% saline. In Pacu patients received i.v. ketorolac 30 mg every 6 h to 24 hours the first dose given in PACU, bu were allowed to refuse these schedulled analgesia if they experienced discomfort. Rescue medication consisted of 1 tablet of acetaminophen/hydrocodone was provided after 1 hour if the pain was not relieved to the subjects satisfaction. Between 24-72 hours analgesia was provided at the patients request with ibuprofen 600 mg every 6 h and 1-2 tablets of cetaminphen 325 mg/hydrocodone 10 mg every 4 h.. Duration 72 hours. Concurrent medication/care: All patients received intrathecal hyperbaric bupivacaine 12 mg, fentanyl 15µg and morphine 150 µg as a single injection. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain NRS at 4 hours at 4 hours; Median reported in the graph only
Ketamine group ~2.8; Control~2.9;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 5
- Actual outcome: Pain NRS at 24 hours at 24 hours; Median reported in the graph only
Ketamine group ~2.2; Control~2.3;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 5

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Cumulative ibuprofen dose at 24 hours; Median (interquartile range)
Ketamine group - 3600(1200-4200); Control 3600(2400 -4200);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 5
- Actual outcome: Cumulative acetaminphen/hydrocodone tablets at 24 hours; Median (interquartile range)
Ketamine group - 2(1-4); Control 1(0 -4);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 5

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at 24 hours; Group 1: 27/85, Group 2: 30/89
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 5
- Actual outcome: vomiting at 24 hours; Group 1: 13/85, Group 2: 13/89

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Beaudoin 2014[88]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in USA; Setting: level 1 trauma center and tertiary care referral center
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients were eligible for study inclusion if they were English-speaking, 18 to 65 years old, had moderate to severe acute pain (score of ≥5 out of 10 on the numerical pain rating scale [NRS] with pain duration < 7 days), and had been deemed by their treating EPs to require IV opioid analgesia. Patients who had already received analgesia prior to study enrollment were still study-eligible as long as their NRS scores were ≥5
Exclusion criteria	Patients were excluded if they had neurologic, respiratory, or hemodynamic compromise; had known or suspected allergy to ketamine or morphine, acute psychiatric illnesses, history of stroke, renal impairment (creatinine > 2.0 mg/dL), liver failure, or history of cardiac disease (prior myocardial infarction, angina, cardiac stents, or bypass surgery); were pregnant or breastfeeding; or were unable to provide informed consent
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (range): Group1(morphine and 0.15 mg/) 37.5 (25.5-46); group2 (morphine and 0.3 mg/kg) 32.5 (25.5-41); control 37.5 (31.5-44.0). Gender (M:F): 37/23. Ethnicity: White 38, black 11, Hispanic 6, asian 0, other 5

Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Participants received: morphine and ketamine (0.15 mg/kg or 0.3 mg/kg) In all groups, patients first received IV morphine 0.1 mg/kg up to a dose of 10 mg, followed by the administration of the study medication (ketamine). Ten minutes was allowed to elapse between dosing of morphine and the study medication to monitor for adverse reactions;. Duration post op. Concurrent medication/care: n/a. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Participants received: 1) morphine and 0.9% saline placebo(standard care group), In all groups, patients first received IV morphine 0.1 mg/kg up to a dose of 10 mg, followed by the administration of the study medication (placebo). Ten minutes was allowed to elapse between dosing of morphine and the study medication to monitor for adverse reactions;. Duration post op. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain intensity (SPID-summed pain intensity difference) at post op; Median IQR
Group(0.15mg) - 7(4.3 - 10.8); Group(0.3mg) 7.8(4.8 - 12.8); Control 4.0(1.8 - 6.5);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Amount of Rescue analgesia (morphine equivalents) at post op; Median
Ketamine1 - 5.4; ketamine2 - 4.3; control - 6.1 mg;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Adverse events - Nausea at post op; Group 1: 6/40, Group 2: 3/20
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Adverse events - vomiting at post op; Group 1: 2/40, Group 2: 0/20

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) - Actual outcome: Psychological distress - Dysphoria at post op; Group 1: 5/40, Group 2: 1/20 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Chazan 2010[162]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in Israel; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients scheduled for elective transthoracic MIDCA, OPCAB or lung surgery under general anesthesia were recruited
Exclusion criteria	existing pain pain of neuromuscular or skeletal origin, chronic use of analgesics, congestive heart failure, hepatic or renal failure, mental disturbances and noncoherency, use of neopsychiatry drugs, pregnancy and age <18 or >85
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine 60 (16); morphine 57(18). Gender (M:F): 30/16. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable 3. Type of surgery: Not applicable (transthoracic MIDCAB, OBCAB).
Indirectness of population	No indirectness

Interventions	(n=24) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Morphine+ketamine (1.0 mg + 5 mg respectively/bolus the device had 7 min lockout period, in case of insufficient pain control by PCA im Diclofenac 75 mg was available every 6 hours. Duration up to 3 days. Concurrent medication/care: Each patient received 10 mg oral diazepam the night before the procedure and 1 hour before the operation. general anesthesia consisted of IV fentanyl (up to 20µg/kg) and /or propofol (1.5 mg/kg) for induction, as well as pancuronium (0.1 mg/kg) to facilitate tracheal intubation. Pancuronium (0.07 mg/kg), fentanyl 15 mg/kg) or propofol (20-50 mg/h) were administered as deemed to be necessary by the attending anesthetist for maintaining anesthesia and stable hemodynamic values.. Indirectness: No indirectness (n=22) Intervention 2: Ketamine (IV) and opioid (IV) - Ketamine + opioid. morphine alone 2 mg bolus, the device had 7 min lockout period, in case of insufficient pain control by PCA im Diclofenac 75 mg was available every 6 hours. Duration up to 3 days. Concurrent medication/care: Each patient received 10 mg oral diazepam the night before the procedure and 1 hour before the operation. general anesthesia consisted of IV fentanyl (up to 20µg/kg) and /or propofol (1.5 mg/kg) for induction, as well as pancuronium (0.1 mg/kg) to facilitate tracheal intubation. Pancuronium (0.07 mg/kg), fentanyl 15 mg/kg) or propofol (20-50 mg/h) were administered as deemed to be necessary by the attending anesthetist for maintaining anesthesia and stable hemodynamic values.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus KETAMINE + OPIOID

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain VAS POD3 at POD3; Group 1: mean 1.8 (SD 1.1); n=24, Group 2: mean 2.4 (SD 1.8); n=22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Cumulative morphine usage (mg) at post op up tp 3 days; Group 1: mean 48 mg (SD 34); n=24, Group 2: mean 78 mg (SD 48); n=22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Postoperative diclofenac usage (n) at post op; Group 1: 13/24, Group 2: 11/22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: PONV at post op; Group 1: 10/24, Group 2: 15/22

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Stubhaug 1997[1205]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Norway; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	all included patients were previously healthy (ASA 1 and 2), scheduled for nephrectomy as part of living-donor kidney transplant programme
Exclusion criteria	not specified
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Median (range): ketamine (32-53); placebo(25-66). Gender (M:F): 10/10. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: urology (nephrectomy).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. After induction of anesthesia bu before the surgery patients in the ketamine group received iv bolus of racemic ketamine 0.5 mg kg-1 Followed by continuous infusion of ketamine 2µg kg-1 min-1 for 24 hours. after 24 hours the infusion rate was reduced to 1µg kg-1 min-1 for another 48 hours PCA morphine bolus of 1 mg with a 5 min lockout period. additional morphine was given and recorded by intensive care nurses. Duration 72 hours. Concurrent medication/care: the patients received 10 mg oral

	diazepam for premedication, and iv fentanyl, diazepam, thiopentone and pancuronium, nitrous oxide and isoflurane. before surgical closure of the wound patients received intercostal nerve blockades with 20 ml bupivacaine 5 mg ml-1.. Indirectness: No indirectness (n=10) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. identical volumes of saline. Duration 72 hours. Concurrent medication/care: the patients received 10 mg oral diazepam for premedication, and iv fentanyl, diazepam, thiopentone and pancuronium, nitrous oxide and isoflurane. before surgical closure of the wound patients received intercostal nerve blockades with 20 ml bupivacaine 5 mg ml-1.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Pain VAS 4 hours post op at post op 4 hours; Reported in the graph only
Ketamine group~22; control~25;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: cumulative morphine consumption (mg) 0-24 hours at post op 0-24 hours; reported on the graph only
Ketamine~60, control 65;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: vomiting days 0-2 at 0-2 days; Group 1: 0/10, Group 2: 8/10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Nausea score day 0 at day 0; Group 1: mean 0.2 (SD 0.4); n=10,
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Nausea score day1 at day 1; Group 1: mean 0.2 (SD 0.4); n=10, Group 2: mean 0.8 (SD 0.9); n=10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Nausea score day2 at day 2; Group 1: mean 0.1 (SD 0.3); n=10, Group 2: mean 0.6 (SD 0.7); n=10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Functional measures - Actual outcome: Global assessment score day 3 at post op day 3; Group 1: mean 3.7 (SD 0.5); n=10, Group 2: mean 3 (SD 1.2); n=10 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Global assessment score day 7 at post op day 7; Group 1: mean 3.9 (SD 0.3); n=10, Group 2: mean 3 (SD 0.9); n=10 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Mathisen 1999[680]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Norway; Setting: not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA grade 1-2 patients undergoing elective laparoscopic cholecystectomy.
Exclusion criteria	not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 49 (15). Gender (M:F): 11/49. Ethnicity: not reported
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 3. Type of surgery: lower and upper GI
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. (R) Ketamine 1.0mg/kg pre-

	operatively. Post-operatively, patients administered PCA meperidine by bolus of 0.1mg/kg with lockout of 5 minutes continued for 4 hours. . Duration 4 hours. Concurrent medication/care: Anaesthesia induced with fentanyl and propofol . Indirectness: No indirectness (n=20) Intervention 2: Ketamine (IV) and opioid (IV) - Ketamine + opioid. (R) Ketamine 1.0mg/kg pre-operatively. Post-operatively, patients administered PCA meperidine by bolus of 0.1mg/kg with lockout of 5 minutes continued for 4 hours. . Duration 4 hours. Concurrent medication/care: Anaesthesia induced with fentanyl and propofol . Indirectness: No indirectness (n=20) Intervention 3: Opioid (IV) and placebo - Opioid + placebo. Saline given pre and post-operatively. Post-operatively, patients administered PCA meperidine by bolus of 0.1mg/kg with lockout of 5 minutes continued for 4 hours. . Duration 4 hours. Concurrent medication/care: Anaesthesia induced with fentanyl and propofol . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE (POST-OP) + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: VAS at 4 hours post operative; Mean; , Comments: Pain at 30 minutes post-operative was significantly lower with post-operative ketamine compared to pre-operative ketamine and to placebo. Difference in pain scores at 1 2 3 and 4 hours post operatively were not statistically different. values presented in graph format ; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: Did not answer telephone; Group 2 Number missing: 5, Reason: Did not answer telephone Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: Meperidine consumption at 4 hours post operative; Mean; , Comments: There was no significant difference between groups in meperedine consumption at 4 hours, 24 hours or 7 days post-op; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: Did not answer telephone; Group 2 Number missing: 5, Reason: Did not answer telephone	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Mckay 2007[690]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=42)
Countries and setting	Conducted in Canada; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Until discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients having bowel resection
Exclusion criteria	Not reported
Recruitment/selection of patients	Recruited from outpatients preadmission clinic
Age, gender and ethnicity	Age - Mean (SD): 50 (14). Gender (M:F): 22/19. Ethnicity: Not reported
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. 2.5ug/kg/min ketamine plus PCA morphine 1mg with 6 minute lockout.. Duration n/a. Concurrent medication/care: patients visited twice daily. . Indirectness: No indirectness (n=22) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Saline plus PCA morphine 1mg with 6 minute lockout.. Duration n/a. Concurrent medication/care: patients visited twice daily. Indirectness: No indirectness
Funding	Academic or government funding (Royal University Hospital Founation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain at rest at Unclear; AUC (IQR)

Ketamine: 24.6 (21.1-34.7); Placebo: 22.7 (12.6-38.1) ; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5 Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: PCA morphine at Unclear; p: 0.57, Comments: Median (IQR) Ketamine: 120mg (51-208); Placebo: 76mg (35-198)); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea at Unclear; Group 1: 10/19, Group 2: 16/22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5 Protocol outcome 4: Length of hospital stay - Actual outcome: Length of hospital stay at n/a; p: 0.21, Comments: Median (IQR) Ketamine: 7 days (7-8) Placebo: 6.7 (9-10)); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	Menigaux 2001[706]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Austria, France, USA; Setting: Hospital Ambroise Pare, Boulogne-Billancourt, France
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 - 60 scheduled to undergo elective arthroscopic meniscal surgery
Exclusion criteria	ASA physical status □II, surgery performed under regional anesthesia, history of chronic pain, chronic use of analgesic medications, drug or alcohol abuse, psychiatric disorders, or contraindications to NSAIDs
Recruitment/selection of patients	scheduled to undergo elective arthroscopic meniscal surgery
Age, gender and ethnicity	Age - Mean (SD): Ketamine: 37 ± 9; Placebo: 36 ± 12. Gender (M:F): 33/17. Ethnicity: NA
Further population details	1. Age: <60 years (Ketamine: 37 ± 9; Placebo: 36 ± 12). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I - II). 3. Type of surgery: ortho/large joint replacement (arthroscopic meniscal surgery).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. After anesthetic induction, 0.15 mg/kg ketamine diluted in isotonic sodium chloride solution was injected IV. Duration preoperatively & postoperatively. Concurrent medication/care: Patients were premedicated with 100 mg hydroxyzine orally, 1–2 h before surgery. Analgesia in the PACU was provided by titrating morphine in increments of 3 mg every 5 min until the VAS pain score was ≤ 30mm or the VRS score was ≤ 2. In the ambulatory unit, naproxen sodium, 550 mg orally, was given to all patients. Before discharge from the hospital, patients were instructed to take 550 mg naproxen sodium twice daily and two tablets Di-Antalvic® (400 mg acetaminophen and 30 mg dextro-propoxyphene) every 6 has needed for pain.. Indirectness: No indirectness (n=25) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. After anesthetic induction, a 10-mL syringe containing either isotonic sodium chloride was injected IV. Duration preoperatively & postoperatively . Concurrent medication/care: Patients were premedicated with 100 mg hydroxyzine orally, 1–2 h before surgery. Analgesia in the PACU was provided by titrating morphine in increments of 3 mg every 5 min until the VAS pain score was ≤ 30mm or the VRS score was ≤ 2. In the ambulatory unit, naproxen sodium, 550

	mg orally, was given to all patients. Before discharge from the hospital, patients were instructed to take 550 mg naproxen sodium twice daily and two tablets Di-Antalvic® (400 mg acetaminophen and 30 mg dextro-propoxyphene) every 6 has needed for pain.. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Amount of additional medication use (< 6 hours post op) - Actual outcome: Number of patients requiring additional Morphine titration at Within PACU; Group 1: 3/25, Group 2: 9/25; Comments: P < 0.05 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Nesher 2009[904]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Israel; Setting: Department of cardiovascular and thoracic surgery at the Tel-Aviv Sourasky medical centre.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	patients were eligible for the study if they had been referred for a first time isolated coronary bypass and if their surgeon considered them candidates for a MIDCAB procedure, or if they were to undergo lung surgery
Exclusion criteria	Exclusion criteria were American society of anesthesiologists physical class >=3, emergency operations, Q-wave myocardial infarct occurring during the previous 3 weeks, or poor left ventricular function (eg, ejection fraction<30% by echocardiography or angiography). other exclusion criteria were as follows: a body mass index 35 >kg/m²; past or current neuropathy or psychological disturbancies; use of psychiatric medications, including antidepressants and anti psychotic agents; chronic liver or renal failure requiring dialysis; FEV1/FVC <70 %; allergy to ketamine, morphine, or nonsteroidal anti-inflammatory drugs; clotting abnormalities; platelet count 70,000/µL; WBC count <3000 µL or >14,000/µL; uncontrolled diabetes mellitus or fasting blood glucose >250 g/dL; and evidence of sepsis or infection up to 1 week prior to randomisation. There was no agent restriction.
Recruitment/selection of patients	not stated
Age, gender and ethnicity	Age - Mean (SD): ketamine+morphine group 61(11); morphine 58(12). Gender (M:F): 23/21. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: vascular (Thoracotomy for minimally invasive direct coronarry artery bypass or for lung resection).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Drug injections consisted of 1mg morphine plus 5 mg ketamine bolus (MK). A blinded anesthesiologist prepared the separate syringes based on randomization list and administered the first dose, after which the PCIA device was turned on. the device was preset to deliver similar boluses whenever the patient activated it, controlled by a 7-min lockout period.

	iff the protocol was ineffective to reduce pain VAS by =>2 levels or patients reported no satisfaction of treatment within 30 min of treatment, rescue dose of IM diclofenac, 75 mg was made available by nurses. Duration post surgery. Concurrent medication/care: GA was administered by the same anesthetist , and no regional block was used. induction of standardized anesthesia consisted of IV midazolam, 2 mg; propofol, 1 mg/kg; medium dose fentanyl, 5 to 15 mg µg/kg; and pancuronium, 0.1 mg/kg, to facilitate endotracheal intubation.. Indirectness: No indirectness (n=22) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Drug injections consisted of 1.5mg morphine plus saline infusion (MO). A blinded anesthesiologist prepared the separate syringes based on randomization list and administered the first dose, after which the PCIA device was turned on. the device was preset to deliver similar boluses whenever the patient activated it, controlled by a 7-min lockout period. iff the protocol was ineffective to reduce pain VAS by =>2 levels or patients reported no satisfaction of treatment within 30 min of treatment, rescue dose of IM diclofenac, 75 mg was made available by nurses. Duration post surgery. Concurrent medication/care: GA was administered by the same anesthetist , and no regional block was used. induction of standardized anesthesia consisted of IV midazolam, 2 mg; propofol, 1 mg/kg; medium dose fentanyl, 5 to 15 mg µg/kg; and pancuronium, 0.1 mg/kg, to facilitate endotracheal intubation.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS during 4 h at 4 hours; Group 1: mean 3.7 (SD 0.7); n=21, Group 2: mean 5.6 (SD 1); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: number of people requiring additional im diclofenac at 4 hours; Group 1: 1/21, Group 2: 4/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: adverse events (nausea+vomiting) at 4 hours; Group 1: 1/21, Group 2: 3/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Kapfer 2005[485]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=77)
Countries and setting	Conducted in USA; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	After informed consent, and with institutional approval, we enrolled 77 patients who were ASA physical status I or II, aged 18–65 yr, and scheduled for major elective open abdominal (colectomy by laparotomy), urologic (nephrectomy by lombotomy), or orthopaedic (hip or knee arthroplasty) surgery under general anesthesia
Exclusion criteria	Exclusion criteria included surgery performed with regional anesthesia, history of chronic pain, regular medication with analgesics, drug or alcohol abuse, psychiatric disorders, morbid obesity, and cardiovascular, renal, or hepatic diseases.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine 51(13); Control 49(15). Gender (M:F): 41/24. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: Not applicable (Major surgery).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. ketamine 10 mg over 12 min Subsequently, morphine titration (3 mg every 5 min) was resumed until the VRS was _2 or until 60 min had elapsed after Time 0. Opioid given after the test drugs (i.e., Time 0) was considered supplemental morphine. However, morphine titration was stopped when patients had a respiratory rate _10 breaths/min, the Spo2 as measured by pulse oximeter was _95%, or the sedation score was _2. Otherwise, they were observed until

	reappearance of a VRS pain score _2. . Duration intra+post op. Concurrent medication/care: Patients were given lorazepam 1 mg orally the night before surgery, but no premedication was given on the day of the surgery. General anesthesia was induced with thiopental and atracurium and was maintained with isoflurane in 50% nitrous oxide and sufentanil 0.3–1.3 _g · kg_1 · min_1. No analgesic other than sufentanil was used during surgery. When patients were sufficiently alert and complained of pain (VRS _2), postoperative analgesia was provided by titrating morphine in 3-mg increments every 5 min until adequate pain relief was obtained. . Indirectness: No indirectness (n=21) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. isotonic saline over 12 min Subsequently, morphine titration (3 mg every 5 min) was resumed until the VRS was _2 or until 60 min had elapsed after Time 0. Opioid given after the test drugs (i.e., Time 0) was considered supplemental morphine. However, morphine titration was stopped when patients had a respiratory rate _10 breaths/min, the Spo2 as measured by pulse oximeter was _95%, or the sedation score was _2. Otherwise, they were observed until reappearance of a VRS pain score _2. . Duration intra+postop. Concurrent medication/care: Patients were given lorazepam 1 mg orally the night before surgery, but no premedication was given on the day of the surgery. General anesthesia was induced with thiopental and atracurium and was maintained with isoflurane in 50% nitrous oxide and sufentanil 0.3–1.3 _g · kg_1 · min_1. No analgesic other than sufentanil was used during surgery. When patients were sufficiently alert and complained of pain (VRS _2), postoperative analgesia was provided by titrating morphine in 3-mg increments every 5 min until adequate pain relief was obtained. Patients were given lorazepam 1 mg orally the night before surgery, but no premedication was given on the day of the surgery. General anesthesia was induced with thiopental and atracurium and was maintained with isoflurane in 50% nitrous oxide and sufentanil 0.3–1.3 _g · kg_1 · min_1. No analgesic other than sufentanil was used during surgery. When patients were sufficiently alert and complained of pain (VRS _2), postoperative analgesia was provided by titrating morphine in 3-mg increments every 5 min until adequate pain relief was obtained. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS percentage of patients with little to no pain 1 hour after infusion of test drug at 1 hour after innfusion of test drug; reported in

the graph only Ketamine~85%; Control group~78%; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Supplemental morphine(mg) at post op; Group 1: mean 9 mg (SD 5); n=22, Group 2: mean 17 mg (SD 10); n=21 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting at post op; Group 1: 8/22, Group 2: 4/21 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Ong 2001[946]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Australia; Setting: Royal Adelaide Hospital, Australia
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I and II patients aged 17–50
Exclusion criteria	Not specified
Recruitment/selection of patients	admitted for extraction of wisdom teeth

Age, gender and ethnicity	Age - Mean (SD): Ketamine: 24.1±5.3; Control: 24.1±6.6 . Gender (M:F): Not specified . Ethnicity: NA
Further population details	1. Age: <60 years (Ketamine: 24.1±5.3; Control: 24.1±6.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: Not applicable (extraction of wisdom teeth).
Indirectness of population	Serious indirectness: age category includes ≥ 17
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients received a ketamine bolus of 0.3 mg/kg diluted in 10 mg/ml dilution prior to induction. . Duration Preoperatively. Concurrent medication/care: Rescue medication was given in the form of i.v. fentanyl boluses of 25 □g, oral Panadeine Forte 1 g and Oxycodone 10 mg.. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients received a corresponding volume of normal saline prior to induction.. Duration Preoperatively. Concurrent medication/care: Rescue medication was given in the form of i.v. fentanyl boluses of 25 µg, oral Panadeine Forte 1 g and Oxycodone 10 mg.. Indirectness: Serious indirectness; Indirectness comment: age range includes ≥ 17
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Mean Fentanyl Dose (< 6 hours) at Prior to discharge; Group 1: mean 60 Micrograms (SD 37.9); n=20, Group 2: mean 86.1 Micrograms (SD 89.3); n=20
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain Score (< 6 hours) at Prior to discharge; Group 1: mean 2.1 Pain score (SD 2.05); n=20, Group 2: mean 3.1 Pain score (SD 2.19); n=20; Visual Analogue Scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Number of patients requiring additional pain relief (< 6 hours) at Prior to discharge; Group 1: 17/20, Group 2: 15/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Vomiting at Postoperatively; Group 1: 7/20, Group 2: 7/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Length of hospital stay - Actual outcome: Discharge Time (minutes) at Postoperatively; Group 1: mean 121.5 minutes (SD 26.8); n=20, Group 2: mean 143.6 minutes (SD 56.8); n=20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Kim 2013[525]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in South Korea; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	After receiving written informed consent, 60 healthy patients with an American Society of Anesthesiologists physical status classification of I-II, aged between 28 and 70 years old, and who were scheduled for elective major lumbar spinal surgery were enrolled in this randomized, placebo-controlled, double-blinded study. The type of surgery was posterior decompression and posterior lumbar interbody fusion with instrumentation.
Exclusion criteria	The exclusion criteria comprised pregnancy,psychiatric problems, chronic alcoholism, drug abuse, inability to use PCA, andlack of communication ability.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Ketamine 56.03(9.627); Control 56(13). Gender (M:F): 24/28. Ethnicity: not stated

Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (elective lumbar spinal fusion).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine infusion of 1 µg/kg/min following bolus 0.5 mg/kg or infusion of 2 µg/kg/min following bolus 0.5 mg/kg of ketamine, started before skin incision intraoperatively, and continued for 48 hours. Post-operatively patients were administered fentanyl using IV-PCA (bolus dose 15 µg of fentanyl, lockout interval of 5 min, no basal infusion).. Duration 48 hours. Concurrent medication/care: Approximate ten minutes before the end of surgery, a 50-100 µg bolus dose of fentanyl and 30 mg ketorolac were given intravenously.. Indirectness: No indirectness (n=17) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Saline bolus plus continuous infusion started before skin incision intraoperatively, and continued for 48 hours. Post-operatively patients were administered fentanyl using IV-PCA (bolus dose 15 µg of fentanyl, lockout interval of 5 min, no basal infusion).. Duration 48 hours. Concurrent medication/care: Approximate ten minutes before the end of surgery, a 50-100 µg bolus dose of fentanyl and 30 mg ketorolac were given intravenously.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain (VAS) at <6 hours; Group 1: mean 6.3 (SD 2.34); n=35, Group 2: mean 6.8 (SD 1.85); n=17; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 3
- Actual outcome: Pain (VAS) at 24 hours; Group 1: mean 3.64 (SD 1.63); n=35, Group 2: mean 4.6 (SD 2.3); n=17; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 3

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Total consumption of fentanyl (µg) at 48 hours; Group 1: mean 619 ug (SD 369.3); n=35, Group 2: mean 826 ug (SD 390); n=17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 3

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)

- Actual outcome: Nausea at 48 hours; Group 1: 10/35, Group 2: 6/17 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 3 - Actual outcome: Vomiting at 48 hours; Group 1: 2/35, Group 2: 1/17 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Pacreu 2012[955]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=22)
Countries and setting	Conducted in Spain; Setting: Tertiary Hospital, Spain
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I - III scheduled for multi-level lumbar arthrodesis
Exclusion criteria	severe COPD, severe heart disease, liver disease, renal impairment, allergy to any of the study medications, psychiatric illness, a known history of alcohol abuse or obesity, treatment with another NMDA receptor antagonists, or use of TCA/SSRI/Anti-convulsant medication.
Recruitment/selection of patients	scheduled for multi-level lumbar arthrodesis
Age, gender and ethnicity	Age - Mean (SD): Ketamine-Methadone: 52.90 ± 12.62; Methadone: 61.30 ± 11.66. Gender (M:F): 14/6. Ethnicity: NA
Further population details	1. Age: >60 years (Ketamine-Methadone: 52.90 ± 12.62; Methadone: 61.30 ± 11.66). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I:3; ASA II: 13; ASA III:4). 3. Type of surgery: ortho/large joint replacement (multi-level lumbar arthrodesis).

Indirectness of population	--
Interventions	(n=11) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Pre-incisional bolus of IV racemic Ketamine 0.5mg/kg, followed by an infusion of 2.5 micrograms/kg/minute.. Duration pre, intra and postoepratively. Concurrent medication/care: Patients given a PCA pump that could deliver bolus of 1ml (0.25mg of methadone + 0.5mg Ketamine) with a lock out period of 10 minutes and a maximum of 3 boluses per hour. . Indirectness: No indirectness (n=11) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Pre-incisional bolus of saline, followed by a saline infusion. Duration pre, intra and postoperatively. Concurrent medication/care: Patients given a PCA pump that could deliver bolus of 1ml (0.5mg of methadone) with a lock out period of 10 minutes and a maximum of 3 boluses per hour. . Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score (recovery room) at < 6 hours postoperatively; Median (IQR): Methadone - Ketamine: 6 (4.25-8); Methadone: 7 (3.5-9) Numerical rating scale 0-10 Top=High is poor outcome, Comments: p value 0.40;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Emergency reoperation ; Group 2 Number missing: 1, Reason: surgeon withdrew PCA

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Methadone consumption at < 6 hours postoperatively; Median (IQR) : Methadone - Ketamine: 3.5 (0.5 - 5.5) ; Methadone: 4 (0.5 - 5.5) Milligrams, Comments: p value 1.0);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Emergency reoperation ; Group 2 Number missing: 1, Reason: surgeon withdrew PCA

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Methadone consumption at 24 hours postoperatively; Median (IQR): Methadone - Ketamine: 3.43 (1.9-6.5); Methadone: 15 (9.65-17.38) Milligrams, Comments: p value < 0.001);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Emergency reoperation ; Group 2 Number missing: 1, Reason: surgeon withdrew PCA

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Burstal 2001[135]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in Australia; Setting: department of anesthesia
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	All patients presenting for total abdominal hysterectomy were considered eligible.
Exclusion criteria	Those receiving opioids preoperatively; undergoing surgery for malignancy, with a history of psychiatric illness or delirium, and of ASA grade greater than 2 preoperative assessment
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Median (range): morphine 45(7) ketamine 43 (10). Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 4 (ASA 3 and 4). 3. Type of surgery: gynae-oncology (hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA morphine 1mg/ml and ketamine 2 mg/ml. PCA was commenced on return of cognitive function.. Duration 48 h postoperatively. Concurrent medication/care: induction with propofol, muscle relaxation with vecuronium and intraoperative analgesia with IV morphine (up to 02 mg/kg, Anaesthesia was maintained with air/oxygen/isoflurane and reversal of muscle relaxation achieved with neostigmine and atropine. Boluses of Morphine were given in recovery as required prior to PCA (1 ml bolus and five minute lockout interval).. Indirectness: No indirectness (n=33) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA morphine 1 mg/ml. Duration 48 h postoperatively. Concurrent medication/care: induction with propofol, muscle relaxation with vecuronium and

	intraoperative analgesia with IV morphine (up to 02 mg/kg, Anaesthesia was maintained with air/oxygen/isoflurane and reversal of muscle relaxation achieved with neostigmine and atropine. Boluses of Morphine were given in recovery as required prior to PCA (1 ml bolus and five minute lockout interval).. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain (patient satisfaction) VAS day 1 (median) at day 1; median (interquartile range)
Ketamine group 8 ; Morphine 8.5;
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain (patient satisfaction) VAS day 2 (median) at day 2; median (interquartile range)
Ketamine group 8.5; Morphine 10;
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain (at rest) VAS day 2 (median) at day 2; Median
Ketamine -2; Morphine - 2;
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain (at rest) VAS day 1 (median) at day 1; median
ketamine - 2; Morphine - 3;
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: nausea at postoperatively; Group 1: 2/37, Group 2: 1/33
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcome 3: Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS))
- Actual outcome: dysphoria (number of people) at postoperatively; Group 1: 4/37, Group 2: 0/33
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Hayes 2004[387]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Australia; Setting: tertiary referral hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	patients who had lower limb amputation because of peripheral vascular disease, cancer or chronic infection
Exclusion criteria	Patients were excluded if they were unable to give informed consent, had severe ischaemic heart disease or were considered unsuitable for general anaesthesia with endotracheal intubation.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine group 68.7 (12.2); Placebo 68.9 (10.9). Gender (M:F): 26/19. Ethnicity: NA
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (lower limb amputation).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. The KG patients recieved apre-induction intravenous (IV) bolus of ketamine 0.5mg.kg-1, followed immediately by IV infusion at 0.15 mg.kg-1.h-1 All patients received PCA with morphine (1 mg bolus, 5 min lockout). Duration pre and post surgery. Concurrent medication/care: All patients received standardized general anaesthetic (midazolam 0.025 mg.kg-1, morphine 0.05 mg.kg-1, thiopentone 1-5 mg.kg-1, endotraheal intubation and intermittent positive pressure ventilation with oxygen, nitrous oxide and isoflurane) After induction additional opioids were given at anaesthetist's discretion. . Indirectness: No indirectness (n=23) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group patients received a pre-

	induction IV bolus of normal saline followed by IV infusion. All patients received PCA with morphine (1 mg bolus, 5 min lockout). Duration pre and post surgery. Concurrent medication/care: All patients received standardized general anaesthetic (midazolam 0.025 mg.kg-1, morphine 0.05 mg.kg-1, thiopentone 1-5 mg.kg-1, endotraheal intubation and intermittent positive pressure ventilation with oxygen, nitrous oxide and isoflurane) After induction additional opioids were given at anaesthetist's discretion. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Median pain thresholds on the stump at day 3 postoperatively; p: 0.12, Comments: median pain thresholds on the stump
Ketamine group - 5.18 units (IQR 1.23)
Control group - 5.88 units (IQR 1.07));
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 4
- Actual outcome: Median pain thresholds on the stump at day 6 postoperatively; Mean; (p: 0.37), Comments: median pain thresholds on the stump
Ketamine - 5.18 (IQR 0.81)
Control - 5.07 (IQR 0.72));
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 4

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: median morphine use at 72 hours at 72 hours postoperatively; p: 0.34, Comments: Median morphine
Ketamine group 118 mg IQR 86
Control 72 mg IQR 100);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 4
- Actual outcome: median morphine use at 24 hours at 24 hours postoperatively; p: 0.61, Comments: Median morphine
Ketamine 44 mg, IQR 32
Control 42 IQR 47);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 4

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental

	wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Yeom 2012[1401]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in South Korea; Setting: department of anesthesiology
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Forty patients between the ages of 38-78 years undergoing 1-2 level posterior lumbarspinal fusion were enrolled in this study. All of the patients were AmericanSociety of Anesthesiologists physical status classification 1, 2, or 3.
Exclusion criteria	Patients with a body mass indexes (BMI) ≥ 30 wereexcluded from the study
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine 61(10); control 64.5(11.5). Gender (M:F): 12/28. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2 and 3). 3. Type of surgery: ortho/large joint replacement (spinal fusion).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. intravenous PCA consisting of fentanyl 0.4 µg/ml/kg with ketamine 30 µg/ml/kg (ketamine group) . Duration intra and post op. Concurrent medication/care: Enrolled patients were not premedicated and each of them received general balanced anesthesia with sevoflurane-N2O-oxygen and continuous infusion of remifentanil. Trachealm intubation was performed under thiopental sodium 4-5 mg/kg, rocuronium 0.6-0.7 mg/kg and sevoflurane inhalation.. Indirectness: No indirectness

	(n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA consisting either of fentanyl 0.4 µg/ml/kg . Duration intra and post op. Concurrent medication/care: Enrolled patients were not premedicated and each of them received general balanced anesthesia with sevoflurane-N2O-oxygen and continuous infusion of remifentanil. Trachealm intubation was performed under thiopental sodium 4-5 mg/kg, rocuronium 0.6-0.7 mg/kg and sevoflurane inhalation.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain NRS at rest 1h in Pacu at 1 h in PACU; Group 1: mean 5.1 (SD 2); n=20, Group 2: mean 8.2 (SD 1.5); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain NRS at rest POD1 at POD1; Group 1: mean 3.6 (SD 2); n=20, Group 2: mean 5.1 (SD 2.1); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain NRS at rest POD2 at POD2; Group 1: mean 2.4 (SD 1.4); n=20, Group 2: mean 4.2 (SD 2.1); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: mean infusion rate of fentanyl (PCA) 1 h in PACU at 1h in PACU; Group 1: mean 1.5 µg/kg/hr.
(SD 0.5); n=20, Group 2: mean 1.4 µg/kg/hr.
(SD 0.6); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: mean infusion rate of fentanyl (PCA) POD1 at POD1; Group 1: mean 0.6 µg/kg/hr.
(SD 0.2); n=20, Group 2: mean 0.6 µg/kg/hr.
(SD 0.5); n=20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: mean infusion rate of fentanyl (PCA) POD2 at POD2; Group 1: mean 0.5 µg/kg/hr.
(SD 0.1); n=20, Group 2: mean 0.6 µg/kg/hr.

(SD 0.2); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea and vomiting 1h in PACU at 1h in PACU; Group 1: 1/20, Group 2: 2/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Nausea and vomiting POD1 at POD1; Group 1: 3/20, Group 2: 3/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Nausea and vomiting POD2 at POD2; Group 1: 1/20, Group 2: 4/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Haliloglu 2016[371]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Turkey; Setting: Umraniye education and research hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	62 ASA I-II scheduled for elective CS were recruited. nuliparous, 18-35 years, gestation 37-40 weeks, general anesthesia.
Exclusion criteria	History of pelvic surgery, chronic pelvic pain known allergy to of the planned perioperative medications, cardiovascular problems, diabetes melitus and evidence of intrauterine growth restriction. indications for CS

	were cephalopelvic disproportion, breech position, placenta praevia or maternal request.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine group 29.1 (2.2); control 29(2.2). Gender (M:F): all female. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (Cesarean section).
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. For bolus dose 10 ml ketamine (5mg ml-1). For infusion during maintenance 50 ml of ketamine (2 mg ml-1).. ketamine bolus of 0.5 mg kg-1 IV was administered at the time of induction of general anesthesia. After induction, a ketamine infusion of 10µg kg-1 min-1 was started and discontinued at the end of the surgery was started and discontinued at the end of the surgery was started and discontinued at the end of the surgery . Duration post op. Concurrent medication/care: No preanesthetic medication was prescribed. after preoxygenation, anesthesia was induced with 4 mg kg-1 thiopenthal.. Indirectness: No indirectness (n=26) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. For bolus dose 10 ml of normal saline was used . For infusion normal saline was used. . Duration post op. Concurrent medication/care: No preanesthetic medication was prescribed. after preoxygenation, anesthesia was induced with 4 mg kg-1 thiopenthal.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain NRS at 6 hours at 6 hours; Group 1: mean 1.23 (SD 0.91); n=26, Group 2: mean 1.07 (SD 0.97); n=26
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain NRS at 24 hours at 24 hours; Group 1: mean 0.42 (SD 0.5); n=26, Group 2: mean 0.46 (SD 0.51); n=26
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: post op morphine consumption 0-6 hours at 0-6 hours; Group 1: mean 11.3 mg (SD 2.1); n=26, Group 2: mean 16.7 mg (SD 2.4); n=26
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: post op CUMULATIVE morphine consumption at 24 hours at 24 hours; Group 1: mean 25 (SD 3.7); n=26, Group 2: mean 36.4 (SD 3.6); n=26
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: rescue diclofenac 24 hours at 24 hours; Group 1: 10/26, Group 2: 13/26
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea + vomiting at 24 hours; Group 1: 4/26, Group 2: 5/26
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Jaksch 2002[438]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)

Countries and setting	Conducted in Austria; Setting: Department of Anesthesiology and Intensive Care Medicine, Ludwig Boltzmann Institute of Experimental Anesthesiology and Research in Intensive Care Medicine; and †Department of Traumatology, Wilhelminenspital, Vienna, Austria
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Inclusion criteria were age 19 yr or older and ASA physical status I or II. enrolled 30 patients scheduled for elective arthroscopic anterior cruciate ligament repair with or without meniscus repai
Exclusion criteria	Excluded from the study were pregnant and breast-feeding women,as well as patients with a history of substance abuse or chronic analgesic use or those for whom opioids, ketamine, or nonsteroidal antiinflammatory drugs were contraindicated.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine 30(8); control 33(7). Gender (M:F): 15/15. Ethnicity: n/a
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: ortho/large joint replacement (arthroscopic anterior cruciate ligament repair with or without meniscus repair).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients randomized to the Treatment group received an IV bolus of S(□)-ketamine (Ketanest S®; Parke-Davis, Berlin, Germany) after the induction of anesthesia. Thereafter a continuous infusion of the drug was started. For the Ketamine group, the 10-mL syringe contained 5 mg/mL of S(+)-ketamine. . For the continuous infusion, the second syringe, with a capacity of 50 mL, contained 2 mg/mL of S(+)-ketamine During the first postoperative hour, patients with VAS scores >3 received fractionated morphine IV (no more than 2mg per 5min). One hour postoperatively, each patient was connected to a PCA pump, which remained in place until the fifth postoperative day at the latest. Morphine 1.5 mg was administered as abolus every 8 min maximally with no background infusion and no hourly limit. Duration intra and post operative. Concurrent medication/care: After being premedicated with oral midazolam 7.5mg 1 h before skin incision, all patients received a standardized anesthetic regimen. TIVA was induced and maintained with remifentanil 0.5μg · kg□1 · min□1 (range, μg.kg□1 · min□1) and a propofol target controlled infusion (MASTER TCI; Fresenius

	Vial S.A., Brezins, France) at a target concentration of 3 µg/mL (range, 2-4 µg/mL). We maintained blood pressure heart rate at levels within 30% of preoperative values. After we administered rocuronium 0.6 mg/kg, an endotracheal tube was inserted and ventilation was performed with oxygen in air (fraction of inspired oxygen =>30%). Indirectness: No indirectness (n=15) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. The control group received an isotonic sodium chloride solution in both the bolus and the infusion. For the control group, the 10-mL syringe contained isotonic sodium chloride solution. . For the continuous infusion, the second syringe, with a capacity of 50 mL, contained Isotonic sodium chloride. During the first postoperative hour, patients with VAS scores >3 received fractionated morphine IV (no more than 2mg per 5min). One hour postoperatively, each patient was connected to a PCA pump, which remained in place until the fifth postoperative day at the latest. Morphine 1.5 mg was administered as abolus every 8 min maximally with no background infusion and no hourly limit. Duration intra and postoperative. Concurrent medication/care: After being premedicated with oral midazolam 7.5mg 1 h before skin incision, all patients received a standardized anesthetic regimen. TIVA was induced and maintained with remifentanil 0.5µg · kg□1 · min□1 (range, µg.kg□1 · min□1) and a propofol target controlled infusion (MASTER TCI; Fresenius Vial S.A., Brezins, France) at a target concentration of 3 µg/mL (range, 2-4 µg/mL). We maintained blood pressure heart rate at levels within 30% of preoperative values. After we administered rocuronium 0.6 mg/kg, an endotracheal tube was inserted and ventilation was performed with oxygen in air (fraction of inspired oxygen =>30%). Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain at rest (median) at post op; Reported in the graph only
at 1 hours Ketamine group ~2; control~2.1
at 2 hours Ketamine group ~1.2; control~1.3
at 24 hours Ketamine group ~1; control~1.4
at 48 hours Ketamine group ~0.8; control~0.7;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: amount of cumulative morphine 24 hours (median) at first 24 hours post op; median amount
Ketamine group 39 mg; Control group 29;

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: amount of cumulative morphine 1hours (median) at first 1 hours post op; median amount Ketamine group - 12 control group-12; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: nausea+respiratory depression at post op; Group 1: 7/15, Group 2: 4/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Aveline 2006[58]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in France; Setting: N/A
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	69 ASA 1-2, scheduled for elective surgical lumbar discectomy with partial laminectomy and nucleotomy.
Exclusion criteria	age<18 years or >75 years, psychiatric disorders, aLCLCOHOL ABUSE, CHRONIC OPIOID TREATMENT, UNCONTROLLED ARTERIAL HYPERTENSION, RENAL OR HEPATIC HYPERTENSION, RENAL OR HEPATIC INSUFICIENCY, INABILITY TO USE PCA.
Recruitment/selection of patients	N/A
Age, gender and ethnicity	Age - Mean (SD): Ketamine+morphine 48.3(12.3); Ketamine 44.8 (8.4); morphine 44.4 (11.2). Gender (M:F):

	32/36. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: Not applicable (lumbar discectomy).
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Before surgery Morphine+ketamine group received morphine 0.1mgkg-1and ketamine 0.15 mgkg-1. in PACU PCA morphine with 7 min lockout. Duration 24 hours. Concurrent medication/care: All patients were premedicated with oral alprazolam 1mg 1 hour before the surgery. General anesthesia was induced with sufentanil and propofol. Sufentanil 0.03 µg kg-1 was given as rescue medication when insufficient analgesia was noted. . Indirectness: No indirectness (n=23) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Before surgery Morphine group received Morphine 0.1 mgkg-1. In PACU PCA morphine 1mg with 7 min lockout.. Duration 24 hours. Concurrent medication/care: All patients were premedicated with oral alprazolam 1mg 1 hour before the surgery. General anesthesia was induced with sufentanil and propofol. Sufentanil 0.03 µg kg-1 was given as rescue medication when insufficient analgesia was noted.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS 4 hours (ketamine+midazolam vs morphine) at post op 4h; median (25 th - 75th percentile)
Ketamine+midazolam 32 (22-37), Morphine - 46(36-54);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VAS 24 hours (ketamine+meperidine vs morphine) at post op 24h; median (25 th - 75th percentile)
Ketamine+meperidine 29 (23-29), Morphine - 39(32-41);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: cumulative PCA morphine 4 h (ketamine+midazolam vs morphine) at post op 4h; Reported in the graph
ketamine+midazolam ~ 2.5, morphine group ~8;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: cumulative PCA morphine 24 h (ketamine+midazolam vs morphine) at post op 24h; Reported in the graph
ketamine+midazolam ~ 7.5, morphine group ~15;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: PONV (ketamine+midazolam vs morphine) at post op 24h; Group 1: 6/23, Group 2: 10/23 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Perrin 2009[996]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=12)
Countries and setting	Conducted in Australia; Setting: Tertiary Hospital, Victoria, Australia
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	If booked for an elective unilateral, two or three total knee arthroplasty with an ASA I - III
Exclusion criteria	BMI > 50; daily opiate use exceeded a systemic morphine equivalent of 10mg or if a history of psychosis was elicited. Patients were to be withdrawn following randomization if the anesthetist beleived it to be medically inadvisable to proceed with the trial protocol, the anesthetist failed to complete the operative protocol in its entirety, poor pain control during the first 48 hours postop required an alternative analgesic regimen or if a second operation was performed on the ipsilateral knee in the 6 month follow up period.
Recruitment/selection of patients	elective unilateral, two or three total knee arthroplasty
Age, gender and ethnicity	Age - Mean (SD): Ketamine: 65.6 ± 10.2; Placebo: 60.3 ± 11.9. Gender (M:F): 7/5. Ethnicity: NA
Further population details	1. Age: >60 years (Ketamine: 65.6 ± 10.2; Placebo: 60.3 ± 11.9). 2. American Society of Anesthesiologists

	(ASA) Physical Status grade: Not stated / Unclear (ASA I - III). 3. Type of surgery: ortho/large joint replacement (unilateral, two or three total knee arthroplasty).
Indirectness of population	No indirectness
Interventions	(n=5) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine 0.5mg/kg bolus followed by 4 micrograms per kilogram per minute infusion. The infusion commenced before surgical incision and continued until the surgical wound was bandaged or the syring was empty. . Duration Intraoperatively. Concurrent medication/care: Intrathecal injection of 15 mg plain bupivacaine + 100 micrograms morphine was administered for anesthesia. Following the onset of leg weakness, general anesthesia was induced. For postoperative pain relief patients received 750mg paracetamol, PCA morphine 2mg bolus with 10 minute lock out, nurse initiated morphine rescue 2.5mg IV every 10 minutes as required if pain score >8/10 on movement, Ibuprofen 800mg orally as rescue if a delay in PCA dose adjustment by acute pain team was anticipated. . Indirectness: No indirectness (n=7) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Saline 0.5mg/kg bolus followed by saline infusion (equivalent volume to Ketamine infusion). The infusion commenced before surgical incision and continued until the surgical wound was bandaged or the syring was empty. . Duration Intraoperatively. Concurrent medication/care: Intrathecal injection of 15 mg plain bupivacaine + 100 micrograms morphine was administered for anesthesia. Following the onset of leg weakness, general anesthesia was induced. For postoperative pain relief patients received 750mg paracetamol, PCA morphine 2mg bolus with 10 minute lock out, nurse initiated morphine rescue 2.5mg IV every 10 minutes as required if pain score >8/10 on movement, Ibuprofen 800mg orally as rescue if a delay in PCA dose adjustment by acute pain team was anticipated. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Average pain score (rest) at 4-20hours; Group 1: mean 2.2 pain score (SD 1.7); n=5, Group 2: mean 2.2 pain score (SD 1.8); n=7; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: outcome from 4 hours to 20 hours; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Morphine use at 0-24hours; Group 1: mean 39.4 Milligrams (SD 36.5); n=5, Group 2: mean 39 Milligrams (SD 42.2); n=7
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: outcome from 0 to 24 hours ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Morue 2018[759]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=132)
Countries and setting	Conducted in Belgium; Setting: tertiary-level hospital
Line of therapy	Not applicable
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	any female undergoing oocyte retrieval by transvaginal ultrasound-guided ovarian puncture.
Exclusion criteria	allergy or contraindication to the use of ketamine (psychiatric disease, coronary insufficiency, intracranial hypertension, thyroidotoxosis or the presence of raised intraocular pressure)
Recruitment/selection of patients	not stated
Age, gender and ethnicity	Age - Mean (SD): ketamine group 35 (5); control 34(6). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (oocyte retrieval).
Indirectness of population	No indirectness
Interventions	(n=67) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. the ketamine group received conscious sedation with the ketamine infusion and a TCI of remifentanil titrated to maintain a pain VAS equal to or less than 30 mmm. Ketamine at concentration at the concentration of 1mg ml-1 . rapid infusion of ketamine (40 µg kg1 min-1) was administered over 5 min (total dose of 0.2 mg kg-1) followed by continuous infusion at fixed rate of 2.5 µg kg-1 min-1 until the end of surgery. TCI remifentanil was guided by a standardised protocol. A TCI Fresenius Agilia pump using the minto pharmacokinetic model, was used for the remifentanil infusion and the concentration was targeted according to age, weight, height of the patient. a

	concentration of 2 ng ml-1 of remifentanil was established before the start of the procedure, and the surgeon waited until 2 min before the first painful stimulation. this concentration was increased in increments of 1ngml-1 until the pain experienced by the patient was less than 30 mm on VAS. Duration intra and post operative. Concurrent medication/care: All patients received oral premedication with 1 g of paracetamol, 10 mg of butyl-hyoscine and 0.5 mg of alprazolam in the operating room, after intravenous access was established, all patients received 0.033 mg kg-1 midazolam and antemeitc prophylaxis with Dexamethasone IV . Indirectness: No indirectness (n=65) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. the control group received 0.9% saline infusion infusion and a TCI of remifentanil titrated to maintain a pain VAS equal to or less than 30 mmm. TCI remifentanil was guided by a standardised protocol. A TCI Fresenius Agilia pump using the minto pharmacokinetic model, was used for the remifentanil infusion and the concentration was targeted according to age, weight, height of the patient. a concentration of 2 ng ml-1 of remifentanil was established before the start of the procedure, and the surgeon waited until 2 min before the first painful stimulation. this concentration was increased in increments of 1ngml-1 until the pain experienced by the patient was less than 30 mm on VAS.. Duration intra and postoperative. Concurrent medication/care: All patients received oral premedication with 1 g of paracetamol, 10 mg of butyl-hyoscine and 0.5 mg of alprazolam in the operating room, after intravenous access was established, all patients received 0.033 mg kg-1 midazolam and antemeitc prophylaxis with Dexamethasone IV. Indirectness: No indirectness
Funding	Other (department of anesthesiology and the fertility clinic of the Erasme hospital, Brussels, Belgium supported this work.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS start of oocyte retrieval at start of oocyte retrieval; Group 1: mean 16 (SD 20); n=61, Group 2: mean 28 (SD 27); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: Pain VAS middle of oocyte retrieval at middle of oocyte retrieval; Group 1: mean 18 (SD 20); n=61, Group 2: mean 33 (SD 24); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: Pain VAS end of oocyte retrieval at end of oocyte retrieval; Group 1: mean 9 (SD 12); n=61, Group 2: mean 15 (SD 22); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: Pain VAS at Pacu arrival at at PACU arrival; Group 1: mean 18 (SD 23); n=61, Group 2: mean 23 (SD 24); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5

- Actual outcome: Pain VAS at Pacu discharge at at PACU discharge; Group 1: mean 13 (SD 14); n=61, Group 2: mean 11 (SD 11); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: Pain VAS maximum postoperative pain at postoperative; Group 1: mean 21 (SD 21); n=61, Group 2: mean 22 (SD 23); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: Pain VAS at hospital discharge at at hospital discharge; Group 1: mean 17 (SD 21); n=61, Group 2: mean 12 (SD 15); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Piritramide needed in PACU (number of people) at post surgery; Group 1: 18/61, Group 2: 21/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: Other pain killer than piritramide required in pacu at post surgery; Group 1: 3/61, Group 2: 4/60
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: analgesia required in 1 day ward at post surgery; Group 1: 1/61, Group 2: 9/60
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: overall analgesia required in the overall postoperative period at post surgery; Group 1: 18/61, Group 2: 25/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5
- Actual outcome: dose of pritramide needed in PACU (to obtain a pain VAS score less than 30 mm) at post surgery; Group 1: mean 4 (SD 2); n=61, Group 2: mean 4 (SD 2); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: adverse events (nausea) at Please enter a time period.; Group 1: 2/61, Group 2: 8/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 45
- Actual outcome: adverse events (vomiting) at post-operative period; Group 1: 1/61, Group 2: 4/60
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 4: Length of stay in intensive care unit
- Actual outcome: average time of stay in PACU (minutes) at post surgery; Group 1: mean 43 minutes (SD 17); n=61, Group 2: mean 44 minutes (SD 22); n=60

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of hospital stay ; Hospital readmission

Study	**Aveline 2009[57]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in France; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	75 ASA physical status I-III undergoing elective unilateral knee replacement under general anesthesia.
Exclusion criteria	age <18 yrs, previous knee surgery on the same side, body mass index =>40 kgm-2, contraindication to nefopam opioid or NSAID's, chronic liver, cardiac or renal failure, any neurologic or psychiatric disorder, alcohose, and inability to use a PCA
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine 72(9), Placebo 70(7). Gender (M:F): 19/30. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA1,2,3). 3. Type of surgery: ortho/large joint replacement (total knee replacement).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. 20 ml syringe containing 2 mg ml ketamine was administered over 20 min; a second 50 ml syringe containing the same concentration of ketamine was used for continuous infusion. 0.2mgkg-1 ketamine hydrochloride iv infusion at 120 µg kg-1 h-1 and then 60 µkg-1 h-1 until second post operative day PCA morphine 1 mg iv bolus with a 7 min lockout interval, without background infusion and limitation of the maximal dose.

	. Duration intra+post op. Concurrent medication/care: General anesthesia was induced with 1.5-2 mg kg-1 propofol, 1µg kg-1 remifentanil, and a single bolus of cisatracurium 0.15 mgkg-1 was administered for tracheal intubation. . Indirectness: No indirectness (n=24) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. isotonic sodium chloride at the same rates PCA morphine 1 mg iv bolus with a 7 min lockout interval, without background infusion and limitation of the maximal dose.. Duration intra + post op. Concurrent medication/care: General anesthesia was induced with 1.5-2 mg kg-1 propofol, 1µg kg-1 remifentanil, and a single bolus of cisatracurium 0.15 mgkg-1 was administered for tracheal intubation.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 6 hours at 6 hours post op; reported in the graph as median
ketamine group~ 33; control group ~ 40;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1
- Actual outcome: Pain VAS at 24 hours at 24 hours post op; reported in the graph as median
ketamine group~ 23; control group ~ 35;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: cumulative PCA morphine consumption 24 h post op at 24 hours post op; Group 1: mean 39.2 mg (SD 6.5); n=25, Group 2: mean 56.8 mg (SD 5.9); n=23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: mean (intraoperative) remifentanil infusion at post op; Group 1: mean 0.25 µg kg-1
(SD 0.04); n=25, Group 2: mean 0.17 µg kg-1
(SD 0.04); n=24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: PONV at 48 hours post op at 48 hours post op; Group 1: 4/25, Group 2: 9/23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 5: Functional measures
- Actual outcome: Time to maximal knee flexion, days at post op; Group 1: mean 12.2 days (SD 4.3); n=25, Group 2: mean 13.6 days (SD 5.5); n=23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1
- Actual outcome: Time to 90· knee flexion, days at post op; Group 1: mean 9.1 days (SD 4.2); n=25, Group 2: mean 12.3 days (SD 4); n=23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1
- Actual outcome: Time to walk, days at post op; Group 1: mean 5 days (SD 5); n=25, Group 2: mean 8.8 days (SD 5.2); n=23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 6: Length of stay in intensive care unit
- Actual outcome: length of hospital stay at post op; Group 1: mean 12 days (SD 2.5); n=25, Group 2: mean 14.1 days (SD 3.8); n=23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Length of hospital stay ; Hospital readmission

Study	**Zakine 2008[1421]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=81)
Countries and setting	Conducted in France; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a

Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	The inclusion criteria were patients over the age of 18 yr scheduled to undergo major abdominal, urologic, or vascular surgery
Exclusion criteria	Exclusion criteria were history of chronic pain, opioid self-administration, and psychiatric disorder
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Intra group (63(12); Peri group 62(13); control group 62(14). Gender (M:F): 59/18. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2,3). 3. Type of surgery: lower and upper GI (Abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PERI group receiving IV bolus of 0.5 mg/kg of ketamine 10min before the incision t followed by IV infusion of 2 μg □kg-1 □ min□1of ketamine starting after this bolus and continued for 48 h postoperatively In the postanesthesia care unit, when the patient indicated a VAS score ≥ 40, a loading dose of 3 mg of IV morphine was administered, followed by another 3 mg dose, 5 min later if necessary,until a VAS ≥ 40 was achieved. A PCA pump device was then started in all three groups. The PCA contained 1 mg/mL of morphine base and 2.5 mg/50 mL of droperidol. The lockout time was 7 min with no limit dose or background infusion. This PCA regimen was continued for 48 h. . Duration 48 hours. Concurrent medication/care: All patients were premedicated with 1 mg/kg of oral hydroxyzine 1 h before surgery. Anesthesia was induced with sufentanil 0.5 μg/kg, propofol 1.5 mg/kg, and cisatracurium 0.15 mg/kg and was maintained by continuous infusion of sufentanil 0.5 μg kg-1 h-1, inhaled desflurane with a mixture of50% N2O/O2 and cisatracurium. All patients received1 g of IV paracetamol 30 min before the end of the surgical procedure. Paracetamol was administered for at least 48 h (1 g/6 h).. Indirectness: No indirectness (n=27) Intervention 2: Ketamine (IV) and opioid (IV) - Ketamine + opioid. INTRA group receiving an IV bolus of 0.5 mg/kg of ketamine10 min before the incision, followed by an IV infusion of 2 μg kg-1 min-1 of ketamine during surgery,and IV infusion of 50 mL of normal saline for 48 h postoperatively; In the postanesthesia care unit, when the patient indicated a VAS score ≥ 40, a loading dose of 3 mg of IV morphine was administered, followed by another 3 mg dose, 5 min later if necessary,until a VAS ≥ 40 was achieved. A PCA pump device was then started in all three groups. The PCA contained 1 mg/mL of morphine base and 2.5 mg/50 mL of droperidol. The lockout time was 7 min with no limit dose or background infusion. This PCA regimen was continued for 48 h. . Duration 48 hours. Concurrent medication/care: All patients were premedicated with 1 mg/kg of oral hydroxyzine 1 h before surgery. Anesthesia was induced with sufentanil 0.5 μg/kg, propofol 1.5 mg/kg, and

	cisatracurium 0.15 mg/kg and was maintained by continuous infusion of sufentanil 0.5 µg kg-1 h-1, inhaled desflurane with a mixture of50% N2O/O2 and cisatracurium. All patients received1 g of IV paracetamol 30 min before the end of the surgical procedure. Paracetamol was administered for at least 48 h (1 g/6 h).. Indirectness: No indirectness (n=27) Intervention 3: Opioid (IV) and placebo - Opioid + placebo. Control group received Placebo. In the postanesthesia care unit, when the patient indicated a VAS score ≥ 40, a loading dose of 3 mg of IV morphine was administered, followed by another 3 mg dose, 5 min later if necessary,until a VAS ≥ 40 was achieved. A PCA pump device was then started in all three groups. The PCA contained 1 mg/mL of morphine base and 2.5 mg/50 mL of droperidol. The lockout time was 7 min with no limit dose or background infusion. This PCA regimen was continued for 48 h. . Duration 48 hours. Concurrent medication/care: All patients were premedicated with 1 mg/kg of oral hydroxyzine 1 h before surgery. Anesthesia was induced with sufentanil 0.5 µg/kg, propofol 1.5 mg/kg, and cisatracurium 0.15 mg/kg and was maintained by continuous infusion of sufentanil 0.5 µg kg-1 h-1, inhaled desflurane with a mixture of50% N2O/O2 and cisatracurium. All patients received1 g of IV paracetamol 30 min before the end of the surgical procedure. Paracetamol was administered for at least 48 h (1 g/6 h).. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Nausea+ vomiting 24 hours (Peri vs CTRL) at 24 hours; Group 1: 1/23, Group 2: 6/27
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 0
- Actual outcome: Nausea+ vomiting 24 -48 hours (Peri vs CTRL) at 24 - 48 hours; Group 1: 1/23, Group 2: 4/27
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 0
- Actual outcome: Cumulative morphine consumption 48 hours (Peri vs CTRL) at 48 hours; Group 1: mean 27 mg (SD 19); n=23, Group 2: mean 50 mg (SD 21); n=27
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 0
- Actual outcome: pain VAS at 4 hours (Peri vs CTRL) at 4 hours; Reported in the graph
Peri ~ 20; control~40;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 0

- Actual outcome: pain VAS at 24 hours (Peri vs CTRL) at 24 hours; Reported in the graph Peri ~ 10; control~30; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Nausea+ vomiting 24 hours (Intra vs CTRL) at 24 hours; Group 1: 4/27, Group 2: 6/27 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Nausea+ vomiting 24 -48 hours (Intra vs CTRL) at 24 - 48 hours; Group 1: 1/27, Group 2: 4/27 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Cumulative morphine consumption 48 hours (Intra vs CTRL) at 48 hours; Group 1: mean 48 mg (SD 41.5); n=27, Group 2: mean 50 mg (SD 21); n=27 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: pain VAS at 4 hours (Intra vs CTRL) at 4 hours; Reported in the graph only Intra group ~ 25; control group~40; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: pain VAS at 24 hours (Intra vs CTRL) at 24 hours; Reported in the graph only Intra group ~ 15; control group~29; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Unlugenc 2003[1288]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Turkey; Setting: n/a
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	90ASA I-II patients, aged 16-60 yr, scheduled for elective major abdominal surgery with general anesthesia, were enrolled into this study.
Exclusion criteria	Inability to use PCA device, longterm use of opioid medications and a history of chronic pain syndromes
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Morphine group 51 (1.1); Morphine +ketamine 52 (4). Gender (M:F): Define. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA I and II). 3. Type of surgery: lower and upper GI (Major abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. PCA morphine 0.4 mgmL-1 +ketamine 1mgmL-1. First standardized loading dose (0.05 mgkg-1) was given to the patients VRS=>2. Patients were allowed to use bolus doses of their study solution (0.0125 mgkg-1 every 20min without time limit) with the PCA device.. Duration post op. Concurrent medication/care: All patients were premedicated with I.V midazolam 0.1 mgkg-1 60min before operation. anesthesia was performed with thiopethal (5mgkg-1) and maintained with sevoflurane 1.5-2% in a mixture of 66% nitrous oxide and 34% oxygen.. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. PCA morphine 0.4 mgmL-1. First standardized loading dose (0.05 mgkg-1) was given to the patients VRS=>2. Patients were allowed to use bolus doses of their study solution (0.0125 mgkg-1 every 20min without time limit) with the PCA device.. Duration post op. Concurrent medication/care: All patients were premedicated with I.V midazolam 0.1 mgkg-1 60min before operation. anesthesia was performed with thiopethal (5mgkg-1) and maintained with sevoflurane 1.5-2% in a mixture of 66% nitrous oxide and 34% oxygen.. Indirectness: No indirectness

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS 60 min at 60 min post op; Reported in the graph only mean no SD
MOrphine +ketamine group~2.1; morphine group ~2.7;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome: Pain VRS 6 hours at 6 hours; reported in median (range)
Morphine +ketamine group~1 (1-2); Morphine group~ 2(1-3);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain VRS 24 hours at 24 hours; reported in median (range)
Morphine +ketamine group~1 (1-2); Morphine group~ 1(1-2);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Cumulative Morphine consumption 6h at 6 h post op; reported in median (range)
Morphine +ketamine group~14.1 (12-17); Morphine group~ 14.9(14-17);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome: Cumulative Morphine consumption 24 h at 24 h post op; reported in median (range)
Morphine +ketamine group~46.5 (43-51); Morphine group~ 49.0(46-51);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: adverse events Nausea at 24 h post op; Group 1: 5/29, Group 2: 9/29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcomes not reported by the	Quality of life ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and

study	mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Remerand 2009[1050]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=160)
Countries and setting	Conducted in France; Setting: Tertiary Hospital, France
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All adult patients scheduled for a nononcologic Total Hip Arthroplasty between January 2006 and April 2007
Exclusion criteria	1) patient refusal, 2) inability to use a patient-controlled analgesia (PCA) device or numerical rating scale (NRS), 3) chronic treatment with drugs that act on neuropathic pain (gabapentin and clonazepam), 4) chronic oral morphine intake >10 mg a day (or equivalent), 5) chronic subcutaneous fentanyl administration, and 6) contraindication to NSAIDs, paracetamol, or ketamine administration (history of gastric ulcer, allergy, creatinine clearance <30 mL/min, porphyries, or severe hepatic or coagulation disorders).
Recruitment/selection of patients	patients scheduled for a nononcologic Total Hip Arthroplasty
Age, gender and ethnicity	Age - Mean (SD): Ketamine: 64 ± 13; Placebo: 65 ± 14. Gender (M:F): 78/82. Ethnicity: NA
Further population details	1. Age: >60 years (Ketamine: 64 ± 13; Placebo: 65 ± 14). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (Total Hip Arthroplasty).
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Between induction and skin incision, patients received an IV bolus of 0.5 mg/kg ketamine (maximum 50 mg) from the first blinded 5-mL syringe, followed by a 24-h infusion using the second study syringe at 2 mL/h (equivalent to 2 Micrograms/ kg-1/ min-1). Duration intraoperatively to postoperative. Concurrent medication/care: Premedication consisted of 100 mg hydroxyzine or 0.5 mg alprazolam 1 h before anesthesia. Postoperative analgesia was started before skin closure. It included IV paracetamol 1 g and ketoprofen 50 mg every 6 h for 24 h. After tracheal extubation in the recovery room, patients were asked to rate pain intensity on the NRS. If NRS was

	more than 3, morphine titration was performed (2–3 mg every 5 min). Once NRS was <3, the PCA device was connected to the patient for 48 h. It contained morphine 100 mg plus droperidol 5 mg in 100 mL of saline. It delivered 1-mL boluses with a lockout period of 7 min (maximum 15 mg/4 h, no background infusion). On Day 1, oral paracetamol (1 g every 6 h until discharge) and ketoprofen (150 mg twice a day for 1 day) were begun. Preoperative chronic analgesics (NSAIDs, tramadol, and dextropropoxyphene) could be reinstated on patient request. Sublingual ondansetron (4 mg) was given in case of PONV. After PCA removal (when patients no longer required it: between Day 1 and Day 4), 20 mg of oral morphine was given on patient request.. Indirectness: No indirectness (n=80) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients received a similar blinded saline bolus and infusion (equivalent to Ketamine infusion). Duration intraoperatively to postoperative. Concurrent medication/care: Premedication consisted of 100 mg hydroxyzine or 0.5 mg alprazolam 1 h before anesthesia. Postoperative analgesia was started before skin closure. It included IV paracetamol 1 g and ketoprofen 50 mg every 6 h for 24 h. After tracheal extubation in the recovery room, patients were asked to rate pain intensity on the NRS. If NRS was more than 3, morphine titration was performed (2–3 mg every 5 min). Once NRS was <3, the PCA device was connected to the patient for 48 h. It contained morphine 100 mg plus droperidol 5 mg in 100 mL of saline. It delivered 1-mL boluses with a lockout period of 7 min (maximum 15 mg/4 h, no background infusion). On Day 1, oral paracetamol (1 g every 6 h until discharge) and ketoprofen (150 mg twice a day for 1 day) were begun. Preoperative chronic analgesics (NSAIDs, tramadol, and dextropropoxyphene) could be reinstated on patient request. Sublingual ondansetron (4 mg) was given in case of PONV. After PCA removal (when patients no longer required it: between Day 1 and Day 4), 20 mg of oral morphine was given on patient request.. Indirectness: No indirectness
Funding	Academic or government funding (Supported by institutional and/or departmental sources.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain score NRS at 24 hours postoperatively ; Group 1: mean 1.4 pain score (SD 1.4); n=79, Group 2: mean 1.5 pain score (SD 1.2); n=75; Comments: p value 0.81
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 5

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine Consumption at 24 hours postoperatively; Group 1: mean 14 Milligrams (SD 13); n=79, Group 2: mean 19 Milligrams (SD 12); n=75; Comments: p value 0.004

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 5 Protocol outcome 3: Functional measures - Actual outcome: First transfer from bed to chair at postoperatively ; Group 1: mean 2.9 days (SD 1.1); n=79, Group 2: mean 2.9 days (SD 1); n=75; Comments: p value 0.74 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 5 - Actual outcome: First steps at postoperatively ; Group 1: mean 3.5 days (SD 1.2); n=79, Group 2: mean 3.3 days (SD 1.2); n=75; Comments: p value 0.54 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 5 Protocol outcome 4: Length of hospital stay - Actual outcome: Length of stay at postoperatively; Group 1: mean 8.8 days (SD 3.2); n=79, Group 2: mean 8.3 days (SD 1.6); n=75; Comments: p value 0.20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Length of stay in intensive care unit ; Hospital readmission

Study	**Deng 2009[233]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in China; Setting: n/a
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a

Inclusion criteria	Totally 200 patients who underwent major surgery for lower limb fracture were involved
Exclusion criteria	The patients with pregnancy, breast feeding, psychiatric disorders, chronic pain, chronic opioid or ketamine usage, inability for PCA, or any other contraindication to remifentanil/ketamine and participation in other research projects were excluded
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine 49.63 (5.59); control 50.1 (6.3). Gender (M:F): 115/85. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (lower limb fracture surgery).
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients received 0.5 mg/kg ketamine infusion under general anesthesia, and ketamine in a dose of 0.1 mg/ kg or 0.05 mg/kg, or 0.01 mg/kg per hour continuously for 24 hours after surgery. With 20 μg/ml remifentanil in normal saline, postoperative PCA was administered with a background infusion at 2 ml/h following 2 ml as a loading dose and 1ml demand dose with a 3-minute lockout period. Duration intra+post op. Concurrent medication/care: Anesthesia was induced and maintained with propofol, remifentanil and vecuronium. Indirectness: No indirectness(n=50) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group received an equivalent volume of normal saline only With 20 μg/ml remifentanil in normal saline, postoperative PCA was administered with a background infusion at 2 ml/h following 2 ml as a loading dose and 1ml demand dose with a 3-minute lockout period. Duration intra+post op. Concurrent medication/care: Anesthesia was induced and maintained with propofol, remifentanil and vecuronium. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain(at rest) VAS at 24 hours at 24 h; Group 1: mean 1.467 (SD 0.899); n=150, Group 2: mean 2 (SD 1); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: PCA Remifentanil consumption (μg) 24h at 0- 24 h; Group 1: mean 1572 μg (SD 468.5); n=150, Group 2: mean 1838 μg (SD 523); n=50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome: Analgesic interventions 24h at 0- 24 h; Group 1: 41/150, Group 2: 24/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: PCA Remifentanil consumption (µg) 0-12h at 0- 12 h; Group 1: mean 831.7 (SD 195.9); n=150, Group 2: mean 943 (SD 204); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: PCA Remifentanil consumption (µg) 12-24h at 12 - 24 h; Group 1: mean 740 µg (SD 196.7); n=150, Group 2: mean 895 µg (SD 190); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: Length of stay in PACU min at post op; Group 1: mean 63.63 minutes (SD 10.58); n=150, Group 2: mean 61.7 minutes (SD 12); n=50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Hadi 2010[366]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Hungary; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	patients scheduled for posterior lumbar and thoracic spinal fusion surgery. in total 30 adult patients.
Exclusion criteria	n/a

Recruitment/selection of patients	n/aPatients scheduled for posterior lumbar ot thoracic spinal fusion surgery
Age, gender and ethnicity	Age - Range: Ketamine 53-59; Control - 49-58. Gender (M:F): 10/20. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (posterior lumbar and thoracic spinal fusion surgery.).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Anesthesia was pre-induced using remifentanil 1µ/kg in both groups followed by remifentanil infusion at a dose of 0.2µg/kg/minute + racemic ketamine infusion 1 µg/kg/min. Duration post op. Concurrent medication/care: All patients were given midazolam 0.25 mg/kg orally 30 minutes before surgery as a premedication. for induction Propofol 2 mg/ kg IV bolus followed by propofol infusion at dose 6 mg/kg/h and atracurium. sevoflurane was used for all patients.. Indirectness: No indirectness (n=15) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Anesthesia was pre-induced using remifentanil 1µ/kg in both groups followed by remifentanil infusion at a dose of 0.2µg/kg/minute normal saline 0.9% . Duration post op. Concurrent medication/care: All patients were given midazolam 0.25 mg/kg orally 30 minutes before surgery as a premedication. for induction Propofol 2 mg/ kg IV bolus followed by propofol infusion at dose 6 mg/kg/h and atracurium. sevoflurane was used for all patients.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: patients with pain (y/n) at post op 24 hours; Group 1: 5/15, Group 2: 13/15
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: patients with NO pain (y/n) at post op 24 hours; Group 1: 10/15, Group 2: 2/15
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Post op Morphine (mg) 24h at post op 24 hours; Group 1: mean 45 mg (SD 5); n=15, Group 2: mean 60 mg (SD 10); n=15
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Joly 2005[458]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in France; Setting: n/a
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Adult patients who were scheduled to undergo open colorectal surgery lasting at least 2 h were studied in two centers (Hospital Ambroise Pare´, Boulogne, France, and Hoˆpital Saint Andre´, Bordeaux, France). All had American Society of Anesthesiologists physical status I–III.
Exclusion criteria	Patients were excluded from the study when (1) immediate extubation was not planned after surgery; (2) they had chronic inflammatory disease including inflammatory bowel disease; (3) they regularly took analgesics or had used opioids within 12 h of surgery; (4) they had a history of drug or alcohol abuse, psychiatric disorder, or obesity (_ 130% of ideal body weight); (5) they had contraindications to the self-administration of opioids (i.e., unable to understand the patient-controlled analgesia [PCA] device); or (6) they had a condition, such as a psychiatric disorder, acute cardiovascular disorder, or unstable hypertension, for which the use ketamine was contraindicated.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Remifentanil+ketamine 59 (13); Remifentanil 57 (12.55). Gender (M:F): Define. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA

	1,2 and 3). 3. Type of surgery: lower and upper GI (colorectal surgery).
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Remifentanil ketamine: intraoperative infusion of remifentanil at a rate 0.4 g kg-1 min-1 and ketamine Subsequently, within 4 h after tracheal extubation, patients were connected to a PCA device set to deliver 1 mg morphine as an intravenous bolus with a 5-min lockout interval;. Duration intra + post op. Concurrent medication/care: Anesthesia was induced with 6 mg/kg thiopental followed by 0.5 mg/kg atracurium to facilitate orotracheal intubation. Two minutes after the thiopental injection, a 1-_g/kg initial dose of remifentanil was given over 60 s. After tracheal intubation, the patients were ventilated to normocapnia with 50% oxygen and without nitrous oxide. An atracurium infusion was titrated to maintain one twitch in response to a supramaximal train-of-four stimulus at the orbicularis oculi; atracurium was discontinued 15 min before the end of surgery. Anesthesia was maintained with remifentanil per randomized dosing described below and desflurane at an initial end-tidal concentration. Indirectness: No indirectness (n=50) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Remifentanil (0.05 µg kg-1 min-1, or 0.4 µg kg-1 min-1) and saline placebo infusion Subsequently, within 4 h after tracheal extubation, patients were connected to a PCA device set to deliver 1 mg morphine as an intravenous bolus with a 5-min lockout interval; Duration intra+post op. Concurrent medication/care: Anesthesia was induced with 6 mg/kg thiopental followed by 0.5 mg/kg atracurium to facilitate orotracheal intubation. Two minutes after the thiopental injection, a 1-_g/kg initial dose of remifentanil was given over 60 s. After tracheal intubation, the patients were ventilated to normocapnia with 50% oxygen and without nitrous oxide. An atracurium infusion was titrated to maintain one twitch in response to a supramaximal train-of-four stimulus at the orbicularis oculi; atracurium was discontinued 15 min before the end of surgery. Anesthesia was maintained with remifentanil per randomized dosing described below and desflurane at an initial end-tidal concentration. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Cumulative post op morphine consumption at post op 0-48 h; median
Small dose remifentanil 68 (50-91) mg
Large dose remifentanil 86 (59-109) mg
Large remifentanil + ketamine 62 (48-87);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting at post op 0-48 h; Group 1: 7/23, Group 2: 15/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Pain VAS at 4 hours at post op 4 h; reported in the graph only Remifentanil+ketamine group ~22; remifentanil~ 31; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Pain VAS at 24 hours at post op 24 h; reported in the graph only Remifentanil+ketamine group ~38; remifentanil~ 30; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Pain VAS (during peak flow)at 24 hours at post op 24 h; Group 1: mean 36 (SD 20); n=23, Group 2: mean 43 (SD 23.65); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Lahtinen 2004[565]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Finland; Setting: department of anesthesiology and intensive care
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients scheduled for elective CABG with cardiopulmonary bypass and younger than 70 yr of age were

	considered eligible for the study
Exclusion criteria	exclusionof those with sleep apnea syndrome or those receiving drug therapy for mental problems.Patients with low cardiac output syndrome (cardiac index _2.0 L · min_1 · m_2) after cardiopulmonary bypass or who could not be weaned from mechanicalventilation within 12 h of the end of surgery were also excluded, as were thosewho underwent a combined cardiac operation including valvular surgery andpatients operated on with a beating heart (off-pump technique). Patients whounderwent reoperation for bleeding or other reasons were also excluded.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine 59(5); placebo 58(7). Gender (M:F): 80/10. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: vascular (cardiac).
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Immediately after anesthesia induction, patients in the S(_)-ketamine group received a 75 _g/kg bolus of S(_)-ketamine (Ketanest-S; Pfizer, Espoo, Finland) in 15 mL of normal saline. Bolus dosing (15 min) of either S(_)-ketamine was followed by continuous infusion of S(_)-ketamine 1.25 _g · kg_1 · min_1 (3 mL/h, with varying concentrations according to body weight) for 48 h after arrival (Time 0) to the postanesthesia care unit (PACU). A PACU nurse administered oxycodone as 2-mg boluses every 10 min until the VAS score at rest was _3 or until excessive sedation (SAS score _4) or respiratory depression (respiratory rate _8 breaths/min) developed. After opioid titration and repeating the instructions, the patients had access to oxycodone (Oxanest; Leiras, Turku, Finland) with a PCA device (Graseby 3300P; Hoyer, Bremen, Germany) with a standardized protocol: bolus dose, 2 mg; dose duration, 2 min; lockout interval, 13 min (15-min effective lockout time); and no background infusion or upper dose limit. Before tracheal extubation, the nurses in the PACU were allowed to give oxycodone 5 mg IV to facilitate the patient's comfort. This extra bolus dose of oxycodone was also allowed once an hour as a rescue analgesic if pain relief with PCA was insufficient. Duration intra + 48 hours post op. Concurrent medication/care: A standardized anesthesia technique was used for all patients. The anesthetic drug doses were calculated according to body weight, as described previously (4). The operation consisted of a standard midline sternotomy, with harvesting of the saphenous vein and internal thoracic artery as indicated. Propofol sedation (2–4mg · kg□1 ·h□1)was continued in the PACU until the patients' peripheral temperature exceeded 32°C, after which it was discontinued and weaning from mechanical ventilation was begun.. Indirectness: No indirectness (n=51) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Immediately after anesthesia induction, patients in the placebo group patients received a 15-mL bolus of normal saline from a syringe with an

	identical appearance. Bolus dosing (15 min) of placebowas followed by continuous infusion of placebo infusion at the same rate (3 mL/h) for 48 h after arrival (Time 0) to the postanesthesia care unit (PACU). A PACU nurse administered oxycodone as 2-mg boluses every 10 min until the VAS score at rest was _3 or until excessive sedation (SAS score _4) or respiratory depression (respiratory rate _8 breaths/min) developed. After opioid titration and repeating the instructions, the patients had access to oxycodone (Oxanest; Leiras, Turku, Finland) with a PCA device (Graseby 3300P; Hoyer, Bremen, Germany) with a standardized protocol: bolus dose, 2 mg; dose duration, 2 min; lockout interval, 13 min (15-min effective lockout time); and no background infusion or upper dose limit. Before tracheal extubation, the nurses in the PACU were allowed to give oxycodone 5 mg IV to facilitate the patient's comfort. This extra bolus dose of oxycodone was also allowed once an hour as a rescue analgesic if pain relief with PCA was insufficient. Duration inntra+48 hours post op. Concurrent medication/care: A standardized anesthesia technique was used for all patients. The anesthetic drug doses were calculated according to body weight, as described previously (4). The operation consisted of a standard midline sternotomy, with harvesting of the saphenous vein and internal thoracic artery as indicated. Propofol sedation (2–4mg · kg□1 ·h□1)was continued in the PACU until the patients' peripheral temperature exceeded 32°C, after which it was discontinued and weaning from mechanical ventilation was begun.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Pain VAS post op day1 at day 1; Group 1: mean 3.3 (SD 0.2); n=44, Group 2: mean 3.4 (SD 0.2); n=46
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5
- Actual outcome: Pain VAS post op day2 at day 2; Group 1: mean 3.4 (SD 0.2); n=44, Group 2: mean 2.9 (SD 0.4); n=46
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: cumulative oxycodone consumption during first 48 hours at 48h; Group 1: mean 103 mg (SD 44); n=44, Group 2: mean 125 mg (SD 45); n=46
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: nausea+vomiting at 48 h; Group 1: 29/44, Group 2: 20/46

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5 Protocol outcome 4: Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) - Actual outcome: Mini mental state examination at 48 h; Group 1: mean 23 (SD 2.6); n=44, Group 2: mean 23 (SD 2.7); n=46 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5 - Actual outcome: delirium rating scale at 48 h; Group 1: mean 3.4 (SD 0.7); n=44, Group 2: mean 3.1 (SD 0.4); n=46 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Wilder-smith 1998[1357]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Denmark; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	45 ASA physical status I or II patients undergoing elective abdominal hysterectomy via Pfannenstiel incision were prospectively randomized
Exclusion criteria	Exclusion criteria included systemic hypertension, epilepsy, chronic magnesium, hypnotic or analgesic use, and diseases predisposing to altered sensation (e.g., diabetes mellitus, neuropathies).
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): fentanyl 48(8); magnesium 47(6); ketamine 47(8). Gender (M:F): all female. Ethnicity: not stated

Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Three minutes before anesthesiainduction, patients received either 0.5 mg/kg ketamine as a slow (60s) intravenous (IV) injection. Anesthesia was induced with 5 mg/kg of thiopental, followed by 0.1 mg/kg vecuronium IV. After tracheal intubation, anesthesia was maintained with isoflurane in oxygen/nitrous oxide (1:2). Five minutes before skin incision 0.25 mg/kg ketamine, was injected and subsequently repeated at 30-min intervals. The final dose was given approximately 45 min before the end of surgery. Dropout was for operations lastinglonger than 2 h or for unsatisfactory anesthesia (hemodynamic values >20% of baseline for >5 min). Morphine PCA was started 30 min postextubation in the recovery room (loading bolus 40 kg/kg, PCA bolus 25 pg/kg; lockout 5 min, background infusion 15 PLg . kg-i . h-i). Threshold measures, pain VRS, cumulative morphine consumption, and an observer sedation rating score (1 = unrousable, 2 = deeply sedated, 3 = moderate sedation, 4 =minor sedation, 5 = wide awake) were obtained at 1, 4, and 24 h postextubation. PCA morphine was discontinued 24 h postoperatively, and analgesia on the ward continuedwith per OS diclofenac. Duration intraop +post op. Concurrent medication/care: n/a. Indirectness: No indirectness (n=15) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Three minutes before anesthesia induction, patients received either 1.5 pg/kg fentanyl, 0 as a slow (60s) intravenous (IV) injection. Anesthesia was induced with 5 mg/kg of thiopental, followed by 0.1 mg/kg vecuronium IV. After tracheal intubation, anesthesia was maintained with isoflurane in oxygen/nitrous oxide (1:2). Five minutes before skin incision, either 0.75 pg/kg fentanyl, , was injected and subsequently repeated at 30-min intervals. The final dose was given approximately 45 min before the end of surgery. Dropout was for operations lastinglonger than 2 h or for unsatisfactory anesthesia (hemodynamic values >20% of baseline for >5 min). Morphine PCA was started 30 min pos textubation in the recovery room (loading bolus 40 kg/kg, PCA bolus 25 pg/kg; lockout 5 min, background infusion 15 PLg . kg-i . h-i). Threshold measures, pain VRS, cumulative morphine consumption, and an observer sedation rating score (1 = unrousable, 2 = deeply sedated, 3 = moderate sedation, 4 = minor sedation, 5 = wide awake) were obtained at 1, 4, and 24 h postextubation. PCA morphine was discontinued 24 h postoperatively, and analgesia on the ward continued with per OS diclofenac. Threshold and pain. Duration intra+post op. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO	

Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain VRS 4 hours post op (median) at 4 hours post op; median Ketamine group 4 (3-5); Fentanyl group - 4(1-5); Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pain VRS 24 hours post op (median) at 24 hours post op; median Ketamine group 2 (1-3); Fentanyl group - 1(0-3); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: cumulative PCA morphine consumption 4h post op at 4 h post op; Group 1: mean 14.9 mg (SD 2.7); n=15, Group 2: mean 16.9 mg (SD 0.3); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: cumulative PCA morphine consumption 24h post op at 24 h post op; Group 1: mean 55.7 mg (SD 12.4); n=15, Group 2: mean 60.9 mg (SD 0.9); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Suzuki 1999[1221]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=140)
Countries and setting	Conducted in USA; Setting: outpatient surgery
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a

Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	One hundred forty patients of both genders, ASA physical status I or II, who were scheduled for elective out patient surgery were recruited for this randomized,double-blinded, placebo-controlled,four-group parallel study. Written, informed consent approved byour human studies committee wasobtained from each patient.
Exclusion criteria	Exclusion criteria included morbid obesity; a history of psychological problems; the use of drugs that affect the central nervous system; chemical substance abuse; chronic pain; pregnancy; seizure disorders; that affect the central nervous system; chemical substance abuse; chronic pain; pregnancy; seizure disorders; increased intracranial pressure; and cardiovascular,hepatic, renal, or psychiatric disease.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine 35.67(10.72); control 39 (12). Gender (M:F): 87/53. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: Not applicable (elective outpatient surgery).
Indirectness of population	No indirectness
Interventions	(n=105) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine 50 mg/kgIV 75 mg/kg IV or 100mg/kg IV 15 min before the end of the operation. Duration intraop. Concurrent medication/care: Preoperative medication was midazolam 1–2 mg IV. Anesthesia was induced with IV propofol 2–2.5 mg/kg and was maintained with desflurane in a nitrous oxide/oxygen mixture. Tracheal intubation was facilitated by succinylcholine. Muscle relaxation was provided by vecuronius. Indirectness: No indirectness (n=35) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. morphine 50µg/kg with placebo before the end of the surgery. Duration intraop. Concurrent medication/care: Preoperative medication was midazolam 1–2 mg IV. Anesthesia was induced with IV propofol 2–2.5 mg/kg and was maintained with desflurane in a nitrous oxide/oxygen mixture. Tracheal intubation was facilitated by succinylcholine. Muscle relaxation was provided by vecuronium . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at discharge at at discharge; Reported in the graph only
Ketamine~ 29 Control~40;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Morphine requirement (µg/kg) at post op; Group 1: mean 97 µg/kg (SD 82); n=105, Group 2: mean 145 µg/kg (SD 93); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting at post op; Group 1: 28/105, Group 2: 9/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Adam 2005[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in France; Setting: not specified
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	With approval of the local ethics committee and informed consent, we studied ASA physical status I–III patients. All were scheduled to undergo elective total knee arthroplasty with general anesthesia
Exclusion criteria	Exclusion criteria included age younger than 18 yr or older than 80 yr, weight exceeding 100 kg, inability to use patient-controlled analgesia (PCA), contraindications to continuous femoral nerve block (i.e., coagulation defects, infection at puncture site), previous total or unilateral knee arthroplasty, diabetes, severe respiratory insufficiency, renal impairment; psychiatric disorders, chronic opioid use, and history of chronic pain syndromes.
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): Ketamine group 68(8); Control 69(6). Gender (M:F): 13/27. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA I-III). 3. Type of surgery: ortho/large joint replacement (Knee arthroplasty).
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. In patients assigned to the ketamine group, 0.05 mL/kg of the blinded test solution (i.e., ketamine 0.5 mg/kg) was given IV over 2 min just after the orotracheal intubation and before the skin incision.The initial bolus was followed by a maintenance IV infusion of 3 μg·kg□1 ·min□1 of ketamine that was continued until the patient emerged from anaesthesia. subsequently, the infusion rate was reduced to 1.5 μg·kg□1 · min□1 and maintained for 48 h. Patients allocated to the control group were given identical volumes of saline. Pain was initially controlled in the PACU by titrating boluses of 3 mg morphine every 5 min until the visual analog rating scale (VAS) score was □30 mm. Titration was stopped if the sedation score was □2or the respiratory rate was □12 breaths per min. Additionally, patients were given access to a PCA device set to

	deliver 1-mg boluses of IV morphine with a lockout period of 5 min and no background infusion or limits. This PCA regimen was continued for 48 h;no other analgesics were given . Duration 48 h. Concurrent medication/care: All patients were premedicated with hydroxyzine 1–2 mg/kg orally 1–2 h before surgery. The patients were taken to a preoperative block room and vital signs were monitored. Midazolam (0.025 mg/kg IV) was given for sedation. A continuous femoral nerve block was performed using the landmarks suggested by Winnie et al. (12), and a catheter was advanced 10–15 cm into the nerve sheaf. Patients were given 0.3 mL/kg ropivacaine 0.75% through the catheter. Absence of sensory response to cold in the area of the femoral nerve confirmed that the catheter was properly positioned. Anesthesia was subsequently induced with 3–5 mg/kg thiopental, 0.3 μg/kg sufentanil, and 0.5 mg /kg atracurium. The trachea was intubated and controlled ventilation began. Anesthesia was maintained with sufentanil infused at a rate of 0.15 μg·kg□1 ·h□1, which was stopped when the surgeon cemented the knee prosthesis (i.e., approximately 30 min before skin closure) and sevoflurane (0.6%–1.5%) in a mixture of nitrous oxide (50%) with oxygen.. Indirectness: No indirectness (n=21) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients allocated to the control group were given identical volumes of saline. Pain was initially controlled in the PACU by titrating boluses of 3 mg morphine every 5 min until the visual analog rating scale (VAS) score was □30 mm. Titration was stopped if the sedation score was □2or the respiratory rate was □12 breaths per min. Additionally, patients were given access to a PCA device set to deliver 1-mg boluses of IV morphine with a lockout period of 5 min and no background infusion or limits. This PCA regimen was continued for 48 h;no other analgesics were given . Duration 48 h. Concurrent medication/care: All patients were premedicated with hydroxyzine 1–2 mg/kg orally 1–2 h before surgery. The patients were taken to a preoperative block room and vital signs were monitored. Midazolam (0.025 mg/kg IV) was given for sedation. A continuous femoral nerve block was performed using the landmarks suggested by Winnie et al. (12), and a catheter was advanced 10–15 cm into the nerve sheaf. Patients were given 0.3 mL/kg ropivacaine 0.75% through the catheter. Absence of sensory response to cold in the area of the femoral nerve confirmed that the catheter was properly positioned. Anesthesia was subsequently induced with 3–5 mg/kg thiopental, 0.3 μg/kg sufentanil, and 0.5 mg /kg atracurium. The trachea was intubated and controlled ventilation began. Anesthesia was maintained with sufentanil infused at a rate of 0.15 μg·kg□1 ·h□1, which was stopped when the surgeon cemented the knee prosthesis (i.e., approximately 30 min before skin closure) and sevoflurane (0.6%–1.5%) in a mixture of nitrous oxide (50%) with oxygen.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO	

	Protocol outcome 1: Pain (>6-24 hours post op) - Actual outcome: Pain VAS at rest 4 hours (graph) at 4 hours; reported in the graph only ketamine group~23; control~23; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 - Actual outcome: Pain VAS at rest 24 hours (graph) at 24 hours; reported in the graph only ketamine group~35; control~37; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: cumulative morphine consumption at PACU at 48 hours; Group 1: mean 45 mg (SD 20); n=20, Group 2: mean 69 mg (SD 30); n=20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea and vomiting at 48 hours; Group 1: 2/20, Group 2: 3/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 4: Functional measures - Actual outcome: time required to reach 90• of active knee flexion at 48 hours; median (IQR) (25% - 75%) Ketamine - 7(5-11); control - 12(8-45); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Guignard 2002[352]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in France; Setting: n/a

Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	adult patients who were scheduled for open colorectal surgery lasting at least 2 h. All were ASA physical status I–III.
Exclusion criteria	Patients were excluded from the study when: (a) immediate extubation was not planned after surgery, (b) they had chronic inflammatory disease including inflammatory bowel disease, (c) they regularly took analgesics or had used opioids within 12 h of surgery, (d) they had a history of drug or alcohol abuse, psychiatric disorder, or obesity (_130% of ideal body weight), or (e) there were contraindications to the self-administration of opioids (i.e., unable to understand the patient controlled analgesia [PCA] device).
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine - 64(10); control 61(13). Gender (M:F): 25/25. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2,3). 3. Type of surgery: lower and upper GI (Colorectal surgery).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. The initial ketamine dose of 0.15 mg/kg was followed by 2 μg · kg-1 · min-1. Thirty minutes before the anticipated end of surgery,a 0.15-mg/kg bolus of morphine was given IV. During the initial postoperative period, 3 mg of morphine was given IV at 5-min intervals until the behavioral pain score (defined later) was <1 or the VRS was <2. However, morphine administration was discontinued in patients having a sedation score (defined later) of 3 or a respiratory rate of <12 breaths/ min. Subsequently, within 4 h after tracheal extubation, patients were connected to a PCA device set to deliver 1 mg of morphine as an IV bolus with a 5-min lockout interval and no background infusion or limits. This PCA regimen was continued for 24 h after tracheal extubation

	. Duration 24 hours. Concurrent medication/care: Anesthesia was induced with thiopental (6 mg/kg) followed by atracurium (0.5 mg/kg) to facilitate orotracheal intubation. Two minutes after the thiopental injection, a 1-µg/kg initial dose of remifentanil was given for 60 s. After tracheal intubation, the patients were ventilated to normocapnia in 50% oxygen without nitrous oxide. Anesthesia was maintained with desflurane at an end-tidal concentration of 0.5 minimum alveolar anesthetic concentration adjusted for age (18). Remifentanil was infused throughout surgery in all patients; the infusion was started at 0.25 µg · kg-1 · min-1 and subsequently increased stepwise by 0.05-µg · kg-1 · min-1 increments if insufficient anesthesia was suspected. Insufficient anesthesia was defined as a heart rate that exceeded preinduction values by 15% or a systolic arterial blood pressure that exceeded baseline values by 20% for at least 1 min. Indirectness: No indirectness (n=25) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group received equal volume saline Thirty minutes before the anticipated end of surgery,a 0.15-mg/kg bolus of morphine was given IV. During the initial postoperative period, 3 mg of morphine was given IV at 5-min intervals until the behavioral pain score (defined later) was <1 or the VRS was <2. However, morphine administration was discontinued in patients having a sedation score (defined later) of 3 or a respiratory rate of <12 breaths/ min. Subsequently, within 4 h after tracheal extubation, patients were connected to a PCA device set to deliver 1 mg of morphine as an IV bolus with a 5-min lockout interval and no background infusion or limits. This PCA regimen was continued for 24 h after tracheal extubation. Duration 24 hours. Concurrent medication/care: Anesthesia was induced with thiopental (6 mg/kg) followed by atracurium (0.5 mg/kg) to facilitate orotracheal intubation. Two minutes after the thiopental injection, a 1-µg/kg initial dose of remifentanil was given for 60 s. After tracheal intubation, the patients were ventilated to normocapnia in 50% oxygen without nitrous oxide. Anesthesia was maintained with desflurane at an end-tidal concentration of 0.5 minimum alveolar anesthetic concentration adjusted for age (18).. Indirectness: No indirectness

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Cumulative post op (median) morphine consumption 0-4 h at 0-4 hours; Median (interquartile range)
Ketamine 21 (10-23); Control 26 (19-36);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Nausea + vomiting at 24 hours; Group 1: 4/25, Group 2: 5/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Cumulative post op (median)morphine consumption 5-24 h at 0-4 hours; Median (interquartile range)
Ketamine 25 (17-34); Control 42 (22-47);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Cumulative post op (median)morphine consumption 0-24 h at 0-4 hours; Median (interquartile range)
Ketamine 46 (34-58); Control 69 (41-87);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Post op Remifentanil dose (µg kg-1 min-1)

at 24 hours; Group 1: mean 0.21 (µg kg-1 min-1) (SD 0.07); n=25, Group 2: mean 0.28 (µg kg-1 min-1) (SD 0.1); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Webb 2007[1343]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Australia; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients were ASA physical status I–III, aged 19–89 yr, and weighed 41–117 kg. Several surgeons and anesthesiologists managed study subjects and most patients (91%) had upper abdominal incisions.
Exclusion criteria	Exclusion criteria included chronic pain, chronic opioid usage,inability to use a PCA, or any contraindication to tramadol, ketamine, or morphine.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine - 63(15); Control 61(15). Gender (M:F): 74/46. Ethnicity: n/a
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1,2 and 3). 3. Type of surgery: lower and upper GI (Elective major abdominal surgery).
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine group: IV ketamine initial dose of 0.3 mg/kg at anesthetic induction and a ketamine infusion at 0.1 mg kg-1 h-1 for 48 h. In the postanesthesia care unit, patients were given IV morphine boluses according to institutional protocol to achieve a pain score on the 11 point (0–10) verbal rating scale (VRS) of <4. Morphine PCA delivering a 1-mg bolus and 5-min lockout time was connected on discharge from the postanesthesia care unit to manage pain uncontrolled by study medications and continued throughout the 48-h study period. Thus, patients had three separate mechanical infusion devicesduring the study.. Duration intraop + 48 post op. Concurrent medication/care: All patients received an initial tramadol dose after induction (3 mg/kg) and tramadol infusion (0.2 mg kg-1 h-1) for 48 h. Anesthesia was induced with propofol. Muscle relaxation was maintained with atracurium, cisatracurium, or rocuronium. Anesthesia was maintained with isoflurane or sevoflurane, supplemented with intraoperative administration of IV fentanyl and/or morphine . Indirectness: No indirectness (n=64) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Control group: An equivalent volume of normal saline atinduction followed by a normal saline infusion at equivalent rate to maintainblinding. In the postanesthesia care unit, patients were given IV morphineboluses according to institutional protocol to achieve a pain score on the 11point (0–10) verbal rating scale (VRS) of <4. Morphine PCA delivering a 1-

	mgbolus and 5-min lockout time was connected on discharge from the postanesthesiacare unit to manage pain uncontrolled by study medications and continued throughoutthe 48-h study period. Thus, patients had three separate mechanical infusion devicesduring the study.. Duration intraop+48 hours post op. Concurrent medication/care: All patients received an initial tramadol dose after induction (3 mg/kg) and tramadol infusion (0.2 mg kg-1 h-1) for 48 h. Anesthesia was induced with propofol. Muscle relaxation was maintained with atracurium, cisatracurium, or rocuronium. Anesthesia was maintained with isoflurane or sevoflurane, supplemented with intraoperative administration of IV fentanyl and/or morphine . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VRS at 4 hours at 4 hours; Reported in the graph only
Ketamine ~4 control~2;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 6
- Actual outcome: Pain VRS at 24 hours at 24 hours; Reported in the graph only
Ketamine ~1.5 control~1.5;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 6

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea score 0-24h at 24 hours; Median (range)
Ketamine- 1(0-2) control-0(0-2);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 6
- Actual outcome: Nausea score 24-48h at 24-48 hours; Median (range)
Ketamine- 0(0-2) control-0(0-2);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 6

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Ayoglu 2005[61]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Turkey; Setting: Turkey Yuksek Ihtisas Hospital
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 20 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I-II patients scheduled for elective laparoscopic cholecystectomy
Exclusion criteria	history of cardiovascular dysfunction, psychiatric disorder, puomondary, hepatic, or renal dysfunction excluded.
Recruitment/selection of patients	No reported
Age, gender and ethnicity	Age - Other: Mean (SEM): Ketamine 52.9 (3.2); Saling 49.1 (3.7). Gender (M:F): 14/26. Ethnicity: not reported
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1-2). 3. Type of surgery: lower and upper GI
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. IV bolus of 0.5mg/kg ketamine slowly and infusion of 0.15 mg/kg for the next 4 hours.. Duration 20 hours. Concurrent medication/care: PCA started on arrival to recovery room. Device programmed to deliver bolus of 1 mg of morphine on demand with lockout interval of 10 min and maximal 4 h dose of 20 mg. . Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Saline bolus infusion of the same volume. . Duration 20 hours. Concurrent medication/care: PCA started on arrival to recovery room. Device programmed to deliver bolus of 1 mg of morphine on demand with lockout interval of 10 min and maximal 4 h dose of 20 mg. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Post-operative pain (NRS) at 0-20 hours; Mean; Mean (SEM) provided in graph format, Comments: Statistically significant (p<0.05) reduction in pain with ketamine at 2, 3 and 4 hours post-op. No statistical difference at 0, 1 , 8 or 20 hours post-operatively. ; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: cumulative morphine consumption at 2 hours; Group 1: mean 5 mg (SD 0.7); n=20, Group 2: mean 8.1 mg (SD 0.8); n=20; Comments: Measured at 2 hours - values are mean (SEM) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: cumulative morphine consumption at 4-20 hours; Mean; , Comments: Values provided in graph format. No significant difference between groups at 4 or 20 hours.; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: PONV at 20 hours; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Menigaux 2000[705]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in France; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	45 inpatients, ASA physical status I or II, aged 18–65 yr, and scheduled to undergo elective arthroscopic ACLR under general anesthesia, were enrolled in the study
Exclusion criteria	Exclusion criteria included ASA physical status .II, any type of surgery other than ACLR, surgery performed under regional anesthesia, history of chronic pain, regular medication with analgesics, drug or alcohol abuse, psychiatric disorder, and contraindications to the self-administration of opioids (i.e., unable to understand the patient-controlled analgesia [PCA] device).
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Pre gropup 26(6); post 26.6; control 28(7). Gender (M:F): 30/15. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: (elective arthroscopic ACLR (Anterior cruciate ligament repair)).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Pre anesthesia group + post anesthesia group. In the PRE group, the patients received IV ketamine 10 min after the induction of anesthesia but before tourniquet inflation and 10 mL of isotonic sodium chloride solution at the end of surgery after skin closure. In the POST group, the patients received 10 mL of isotonic sodium chloride solution 10 min after the induction of anesthesia but before tourniquet inflation and IV ketamine at the end of surgery. In the PACU, the pain was controlled by a titration of IV morphine administered by a nurse. This titration consisted of repeated boluses of 3 mg of morphine every 5 min until the VRS was <2. The titration was stopped in case of a sedation score >3 or a respiratory rate <12 breaths/min. Subsequently, the patients were given access to a PCA device. The PCA device was set to deliver morphine 1 mg as an IV bolus with an interval of 5 min and no background infusion or limits. This regimen of PCA was continued for 48 h on the surgical ward. acetaminophen, , 1 g every 6 h, was added during the second postoperative day. During physical therapy sessions 24 and 48 h after surgery, patients used IV morphine PCA to provide analgesia. Duration intraop + 48 hours post op. Concurrent medication/care: Patients were premedicated with hydroxyzine 100 mg orally, 1–2 h before surgery. Anesthesia was induced with propofol at an initial target concentration of 5 mg/mL (e.g., 2 mg/kg) and vecuronium 0.1 mg/kg to facilitate placement of a laryngeal mask airway. Anesthesia was maintained with a continuous administration of propofol (target concentration 2–6 mg/mL; e.g., 60–200 mg z kg-1 z min-1) and 60% N2O in O2 during controlled ventilation. The objective was to maintain arterial pressure and

	heart rate within 30% of the preoperative value. A bolus of 0.2 mg/kg sufentanil was administered 10 min after surgical incision, followed by a continuous infusion of 0.25 mg z kg-1 z h-1 that was stopped 30 min before skin closure. Indirectness: No indirectness (n=15) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. In the CONT group, both injections were of isotonic sodium chloride solution. In the PACU, the pain was controlled by a titration of IV morphine administered by a nurse. This titration consisted of repeated boluses of 3 mg of morphine every 5 min until the VRS was <2. The titration was stopped in case of a sedation score >3 or a respiratory rate <12 breaths/min. Subsequently, the patients were given access to a PCA device. The PCA device was set to deliver morphine 1 mg as an IV bolus with an interval of 5 min and no background infusion or limits. This regimen of PCA was continued for 48 h on the surgical ward. acetaminophen, , 1 g every 6 h, was added during the second postoperative day. During physical therapy sessions 24 and 48 h after surgery, patients used IV morphine PCA to provide analgesia.. Duration Intraop+48 hours post op. Concurrent medication/care: Patients were premedicated with hydroxyzine 100 mg orally, 1–2 h before surgery. Anesthesia was induced with propofol at an initial target concentration of 5 mg/mL (e.g., 2 mg/kg) and vecuronium 0.1 mg/kg to facilitate placement of a laryngeal mask airway. Anesthesia was maintained with a continuous administration of propofol (target concentration 2–6 mg/mL; e.g., 60–200 mg z kg-1 z min-1) and 60% N2O in O2 during controlled ventilation. The objective was to maintain arterial pressure and heart rate within 30% of the preoperative value. A bolus of 0.2 mg/kg sufentanil was administered 10 min after surgical incision, followed by a continuous infusion of 0.25 mg z kg-1 z h-1 that was stopped 30 min before skin closure. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain VAS at 3 hours at at 3 hours; Reported in the graph only
Pre ~3.2; Post~2.8; control~3.3
;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain VAS at 24 hours at at 24 hours; Reported in the graph only
Pre ~32.4; Post~2.5; control~4.2;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: cumulative morphine consumption at 24 hours at at 24 hours; Group 1: mean 26.2 mg (SD 18.21); n=30, Group 2: mean 49.7 mg (SD 24.1); n=15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Morphine use POD1 at POD1; Group 1: mean 1.3 mg (SD 0.579); n=30, Group 2: mean 3.8 mg (SD 1.7); n=15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Morphine use POD2 at POD2; Group 1: mean 0.4 mg (SD 0.5); n=30, Group 2: mean 0.6 mg (SD 0.7); n=15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Functional measures - Actual outcome: maximal knee flexion (°) POD1 at post op POD1; Group 1: mean 66.5 (°) (SD 6.103); n=30, Group 2: mean 62 (°) (SD 11); n=15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pain (VRS) POD 1 at post op POD1; Group 1: mean 2.35 (SD 0.512); n=30, Group 2: mean 2.9 (SD 0.4); n=15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pain (VRS) POD 2 at post op POD2; Group 1: mean 1.85 (SD 0.808); n=30, Group 2: mean 1.8 (SD 0.5); n=15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: maximal knee flexion (°) POD2 at post op POD2; Group 1: mean 83 (SD 8.631); n=30, Group 2: mean 81 (SD 11); n=15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Moro 2017[756]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=135)

Countries and setting	Conducted in Brazil; Setting: Santa Lucinda hospital Brazil
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	135 patients aged 18-65 years old, With an ASA Physical status I or II, who where scheduled to undergo laparoscopic cholecystectomy from July 2015 to February 2016 were included
Exclusion criteria	Refusal to participate; altered level of conciousness or inability to communicate; presented with contraindication to any of the drugs used in the study; history of alcohol or drug abuse and body mass index (BMI) ≥40. Reasons for exclusion following randomisation included: protocol violations such as the use of medications not contemplated in the study protocol; conversion to an open surgical technique
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketmine - 45.53(12.41; Control - 41.8(11.3). Gender (M:F): 17/102. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: lower and upper GI (Laparoscopic cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=90) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Immediately following anesthetic induction, Ketamine(0.2mg/kg or 0.4 mg/kg) was administered. In Pacu morphine(1-2mg) was administered iv every 10 min to maintain pain score below 4 (1 mg when the pain score was <7 and 2 mg when it was ≥7. Following discharge from the PACU (minimum stay 60 min and Aldrete score ≥9), all of the participants were given ketoprofen (100mg) every 12 hours and dipyrone (30 mg/kg, maximum 1 g every 6h IV. Whenever patients judged their analgesia to be insufficient, tramadol (100mg) was administered IV at eight-hour minimum intervals.. Duration intraoperatively + in PACU. Concurrent medication/care: Standard ASA monitors were applied upon entry into the operating room followed by administration of Midazolam 0.06 mg/kg and 1 % lidocaine (30 mg).Anesthesia was induced with Remifentanil 0.5 µg/kg/min over 3 min followed by propofol 0.2 mg mg/kg. Rucoronium 0.6 mg/kg was administered to facilitate tracheal intubation. Anesthetic maintenance was achieved with continuous infusion of Remifentanil 0.3 µg/kg/min and propofol 4-6 mg/kg/h. Normal saline was used for fluid replacement therapy at a rate of 500 ml throughout the first 30 min, and, then 2ml/kg/h until the end of surgical procedure. All of the participants were given dexamethasone (8mg) and ketoprofen (100mg) at onset of surgery and dimenhydrinate (30mg), dipyrone 1 g) and morphine (0.1 mg/kg) 15 min prior to the procedure. Atropine (0.01 mg/kg)were used to achieve T4/T1 >0.9 on the TOF monitor prior to extubation.. Indirectness: No indirectness

	(n=45) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Immediately following anesthetic induction, Normal saline was administered. In Pacu morphine(1-2mg) was administered iv every 10 min to maintain pain score below 4 (1 mg when the pain score was <7 and 2 mg when it was ≥7. Following discharge from the PACU (minimum stay 60 min and Aldrete score ≥9), all of the participants were given ketoprofen (100mg) every 12 hours and dipyrone (30 mg/kg, maximum 1 g every 6h IV. Whenever patients judged their analgesia to be insufficient, tramadol (100mg) was administered IV at eight-hour minimum intervals.. Duration Intraoperatively + in PACU. Concurrent medication/care: Standard ASA monitors were applied upon entry into the operating room followed by administration of Midazolam 0.06 mg/kg and 1 % lidocaine (30 mg).Anesthesia was induced with Remifentanil 0.5 µg/kg/min over 3 min followed by propofol 0.2 mg mg/kg. Rucoronium 0.6 mg/kg was administered to facilitate tracheal intubation. Anesthetic maintenance was achieved with continuous infusion of Remifentanil 0.3 µg/kg/min and propofol 4-6 mg/kg/h. Normal saline was used for fluid replacement therapy at a rate of 500 ml throughout the first 30 min, and, then 2ml/kg/h until the end of surgical procedure. All of the participants were given dexamethasone (8mg) and ketoprofen (100mg) at onset of surgery and dimenhydrinate (30mg), dipyrone 1 g) and morphine (0.1 mg/kg) 15 min prior to the procedure. Atropine (0.01 mg/kg)were used to achieve T4/T1 >0.9 on the TOF monitor prior to extubation.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain NRS (in PACU) at <6 hours; Group 1: mean 3.23 (SD 2.936); n=80, Group 2: mean 3.2 (SD 2.8); n=39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 6

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain NRS (in PACU) at 24 hours; Group 1: mean 38 (SD 2.327); n=80, Group 2: mean 39 (SD 2.1); n=39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 6

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine consumption at 24 hours; Group 1: mean 1.2 mg (SD 1.947); n=80, Group 2: mean 1.6 mg (SD 2.2); n=39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 6
- Actual outcome: Tramadol consumption at 24 hours; Group 1: mean 5.075 mg (SD 12.6); n=80, Group 2: mean 2 mg (SD 5.1); n=39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 6 Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea and vomiting at 24 hours; Group 1: mean 14.23 (SD 35.43); n=80, Group 2: mean 12 (SD 30.8); n=39 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 6 Protocol outcome 5: Length of stay in intensive care unit - Actual outcome: length of stay in PACU(minutes) at 24 hours; Group 1: mean 85.31 minutes (SD 27.37); n=80, Group 2: mean 82.9 minutes (SD 23.9); n=39 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 6	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of hospital stay ; Hospital readmission

Study	**Han 2013[377]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in South Korea; Setting: Department of anesthesiology and Pain medicine
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	The study was conducted on 40 pregnant mothers of ASA class 1-2, between 37-42 weeks of pregnancy, who were scheduled for cesarean section under spinal anesthesia.
Exclusion criteria	Patients with psychological diseases, difficulties communicating, allergies to local anesthesia, inflammation in the spinal puncture area, coagulation disorder, administered analgesics, and those who underwent an emergency operation were excluded.

Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): Ketamine 32.7(3.7); Control 32.5(3.6). Gender (M:F): all female. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (Caesarean section).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients in the ketamine group received a 0.5 mg/kg ketamine bolus intravenously followed by 0.25 mg/kg/h continuous infusion during the operation. Immediately after surgery, the patients were connected to a PCA device set to deliver 25-ìg fentanyl as an intravenous bolus with a 15-min lockout interval and no continuous dose. Duration intra+postop. Concurrent medication/care: No premedication was administered, and patients were monitored by electrocardiogram, non-invasive arterial blood pressure, and pulse oximetry when they entered the operating room. In the left lateral decubitus position, the dura was punctured between the L3-4 intervertebral space using a 24-gauge Quincke spinal needle. After checking for cerebrospinal fluid, 10 mg 0.5% hyperbaric bupivacaine (Marcaine Spinal Heavy, AstraZeneca, UK) was injected. When systolic blood pressure decreased to < 90 mmHg, or 30% of the pre-anesthetic blood pressure, it was corrected by administering 5 mg ephedrine or 50 ìgphenylephrine. Indirectness: No indirectness (n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. The control group received the same volume of normal saline. Immediately after surgery, the patients were connected to a PCA device set to deliver 25-ìg fentanyl as an intravenous bolus with a 15-min lockout interval and no continuous dose. Duration intra+post op. Concurrent medication/care: No premedication was administered, and patients were monitored by electrocardiogram, non-invasive arterial blood pressure, and pulse oximetry when they entered the operating room. In the left lateral decubitus position, the dura was punctured between the L3-4 intervertebral space using a 24-gauge Quincke spinal needle. After checking for cerebrospinal fluid, 10 mg 0.5% hyperbaric bupivacaine (Marcaine Spinal Heavy, AstraZeneca, UK) was injected. When systolic blood pressure decreased to < 90 mmHg, or 30% of the pre-anesthetic blood pressure, it was corrected by administering 5 mg ephedrine or 50 ìgphenylephrine.. Indirectness: No indirectness
Funding	Academic or government funding (This work was supported in part by the Soonchunhyang University Research Fund.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain VAS at 6 h post op at 6 h post op; median

ketamine group 3 (2.8-5); control 3.5 (3-5); Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 - Actual outcome: pain VAS 24 h post op at 24 h post op; median ketamine group 3 (2-4); control 3 (2-4.3); Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: Cumulative dose of Fentanyl (post op) 6h post op at 6 h post op; Group 1: mean 189 (SD 63.1); n=19, Group 2: mean 183 (SD 48.7); n=17 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 - Actual outcome: Cumulative dose of Fentanyl (post op) 24h post op at 24 h post op; Group 1: mean 602.4 (SD 113.8); n=19, Group 2: mean 608.2 (SD 83.7); n=17 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 - Actual outcome: ketorolac use postoperatively (number of patients) at post op; Group 1: 4/19, Group 2: 6/17 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Guillou 2003[353]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in France; Setting: SICU (surgical intensive care unit)
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Adults older than 18 yr were included if they were scheduled to have major abdominal surgery and postoperative management and ventilation in a SICU.
Exclusion criteria	Pregnant women and patients who had severe cardiovascular disorders (ejection fraction □30%) or renal insufficiency(creatinine clearance □30 mL/min), or who were unable to understand the use of patient-controlled analgesia (PCA), were not included.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): ketamine group - 60 (16); Morphine 60 (15). Gender (M:F): 68/31. Ethnicity:
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (major abdominal surgery: hepatectomy, esophageal surgery, others).
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. The PCA device contained morphine at a concentration of 1mg/mL. All patients received initial loading doses of 2 mg of morphine until their VAS score was less than 30; they were then allowed to have bolus doses of morphine (1 mg every 7 min) without any limitation. In Group K, ketamine was administered separately with an initial bolus of 0.5 mg/kg followed by aperfusion of 2 during the first 24 h and 1g · kg□1 ·min□1 in the folg · kg□1 · min□1 lowing 24 h.. Duration 48 h. Concurrent medication/care: Each patient was premedicated with oral midazolam 90 min before the operation. General Anesthesia was induced with propofol (2 mg/kg) orthiopental (10 mg/kg). Anesthesia was maintained with nitrous oxide,isoflurane, sufentanil, and atracurium. A central venous catheter and an arterial radial catheter were inserted. Electrocardiogram, pulse oximetry,capnography, arterial blood pressure, and central venous pressure were continuously monitored. Crystalloids were infused during the surgical procedure if the central venous pressure decreased to less than 3 cm H2O, and packed red bloods cells were administered if the patient's hemoglobin level decreased to less than 7.0 g/dL. At the end of the procedure, no antagonists were used. After the operation, patients were treated in the SICU for at least 48 h.. Indirectness: No indirectness (n=54) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. The PCA device contained morphine at a concentration of 1mg/mL. All patients received initial loading doses of 2 mg of morphine untiltheir VAS score was less than 30; they were then allowed to have bolus doses ofmorphine (1 mg every 7 min) without any limitation. In Group M, ketamine wasreplaced bysaline serum and was administered under the same conditions.Ketamine or placebo was administered simultaneously with the titration ofmorphine. A nurse not involved in the care of the patients prepared thesyringes of ketamine or placebo. No additional analgesia or sedation wasadministered to patients during their SICU stay.. Duration 48 h. Concurrent medication/care: Each patient was premedicated with oral midazolam 90 min before the operation. General Anesthesia was

	induced with propofol (2 mg/kg) orthiopental (10 mg/kg). Anesthesia was maintained with nitrous oxide,isoflurane, sufentanil, and atracurium. A central venous catheter and an arterial radial catheter were inserted. Electrocardiogram, pulse oximetry,capnography, arterial blood pressure, and central venous pressure were continuously monitored. Crystalloids were infused during the surgical procedure if the central venous pressure decreased to less than 3 cm H2O, and packed red bloods cells were administered if the patient's hemoglobin level decreased to less than 7.0 g/dL. At the end of the procedure, no antagonists were used. After the operation, patients were treated in the SICU for at least 48 h.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: pain at 4 hours at 4 hours post op; reported in the graph only
Ketamine group ~42, morphine group~40;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 2
- Actual outcome: pain at 24 hours at 24 hours post op; reported in the graph only
Ketamine group ~38, morphine group~40;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 2

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: cumulative post op PCA morphine use (4h post op) at 4 hours post op; reported in the graph only
Ketamine group ~5mg, morphine group~12;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 2
- Actual outcome: cumulative post op PCA morphine use (24h post op) at 24 hours post op; reported in the graph only
Ketamine group ~38, morphine group~50;
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 2

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at 48 hours post op; Group 1: 2/41, Group 2: 4/52
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 2

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Hadi 2009[365]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Jordan; Setting: Arab center hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	40 patients who had a physical status class I-II ASA, Schedulled for scoliosis surgery
Exclusion criteria	not specified
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Range: ketamine group 20-24, Remifentanil 19-23. Gender (M:F): 15/25. Ethnicity: not stated
Further population details	1. Age: <60 years 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: ortho/large joint replacement (Scoliosis surgery).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Intraoperative bolus dose of 1 µg/kg of remifentanyl was given at induction for both groups followed by a combination of remifentanil infusion in a dose of 0.2 µg/kg/minutes and ketamine infusion in a dose of 1 µg/kg/minutes. Postoperatively morphine infusion pump was set to deliver morphine solution (1 mg/ml) at the rate of 3–5 mg/hr in the PACU.. Duration n/a. Concurrent medication/care: On arrival at the operating theatre, the following drugs were given intraoperatively: propofol 2 mg/kg IV bolus was given for induction in both groups followed by propofol infusion in a dose of 6 mg/kg/h; atracurium 0.6 mg/kg was given to facilitate orotracheal intubation just at the induction; sevoflurane (1–1.5% v/v) was given in a carrier gas of a 1:1 nitrous oxide: oxygen mixture.. Indirectness: No indirectness

	(n=20) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. bolus dose of 1 µg/kg of remifentanyl was given at induction for both groups followed by remifentanil infusion in a dose of 0.2 µg/kg/minutes in. Postoperatively morphine infusion pump was set to deliver morphine solution (1 mg/ml) at the rate of 3–5 mg/hr in the PACU.. Duration n/a. Concurrent medication/care: On arrival at the operating theatre, the following drugs were given intraoperatively: propofol 2 mg/kg IV bolus was given for induction in both groups followed by propofol infusion in a dose of 6 mg/kg/h; atracurium 0.6 mg/kg was given to facilitate orotracheal intubation just at the induction; sevoflurane (1–1.5% v/v) was given in a carrier gas of a 1:1 nitrous oxide: oxygen mixture.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Total morphine consumption at 24 hours; Group 1: mean 45 mg (SD 5); n=20, Group 2: mean 60 mg (SD 10); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: PONV at 24 hours; Mean; , Comments: no differences were noted in the incidence of pruritis, postoperative nausea and vomiting in the two groups.; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Badrinath 2000[66]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in USA; Setting: Department of anesthesiology
Line of therapy	Not applicable

Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	One hundred consenting ASA physical status I and II female outpatients undergoing breast biopsy procedures under local anesthesia were studied
Exclusion criteria	Patients with clinically significant cardiovascular, respiratory, or he- patic diseases were excluded from participating. In addition, patients with a history of drug or alcohol abuse, as well as those currently taking sedative or analgesic drugs, were also excluded. All study patients gave a written informed consent before enrollment.
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): placebo -56(15); propofol/ketamine(10:1) - 53(14); propofol/ketamine(5:1) - 53(12); propofol/ketamine(3.3:1) 49(10). Gender (M:F): all female. Ethnicity: not specified
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 2 (ASA 1 and 2). 3. Type of surgery: gynae-oncology (breast biopsy procedures).
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. propofol/ketamine (10:1; 5:1 or 3.3:1); According to a prestudy randomization schedule of study group assignment, a standard volume of 1.2 mL containing either 0mg, 20 mg, 40mg, or 60 mg ketamine in saline was added to 20 mL of propofol. Thus, the study drug solutions consisted of propofol, 9.4 mg/mL, and ketamine, 0, 0.94, 1.88, or 2.83 mg/mL, respectively. Patients responding with pain □1, discomfort □3, or movement to the of local anesthetic by the surgeon by the surgeon were treated with a “rescue” bolus of sufentanil, 2.5 µg IV. Duration intra and postoperative. Concurrent medication/care: All patients received midazolam, 2 mg IV, for premedication before transfer to the operating room where standard monitoring devices were placed. Indirectness: No indirectness (n=25) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. propofol/placebo; According to a prestudy randomization schedule of study group assignment, a standard volume of 1.2 mL containing either 0mg, 20 mg, 40mg, or 60 mg ketamine in saline was added to 20 mL of propofol. Thus, the study drug solutions consisted of propofol, 9.4 mg/mL, and ketamine, 0, 0.94, 1.88, or 2.83 mg/mL, respectively. Patients responding with pain □1, discomfort □3, or movement to the of local anesthetic by the surgeon by the surgeon were treated with a “rescue” bolus of sufentanil, 2.5 µg IV. Duration intra and postoperative. Concurrent medication/care: All patients received midazolam, 2 mg IV, for premedication before transfer to the operating room where standard monitoring devices were placed. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Amount of additional medication use (>6-24 hours post op) - Actual outcome: overall rescue sufentanil requirements at post op; Group 1: 13/75, Group 2: 17/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Average sufentanil dose per case at post op; Group 1: mean 0.9767 mg (SD 2.367); n=75, Group 2: mean 3.6 mg (SD 3.2); n=25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea+vomiting at post op; Group 1: 24/75, Group 2: 1/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: time to discharge min at post op; Group 1: mean 79.57 min (SD 28.11); n=75, Group 2: mean 66.8 min (SD 17.8); n=25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Gillies 2007[331]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in Australia; Setting: Department of anesthesia
Line of therapy	Not applicable
Duration of study	Intervention + follow up:

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients were eligible for inclusion if they required more than two doses of morphine in the recovery room,, had a pain score >=5 on a standard verbal rating scale (VRS), a sedation score less than or equal to one and a respiratory rate greater than eight.
Exclusion criteria	allergy to morphine, history of major psychiatric disturbance or currently taking psychiatric medications, chronic morphine usage, chronic pain syndrome, unable to gain reliable pain score in recovery due to language barriers or residual anaesthesia, known pregnancy, where the primary anethetist preferred an alternative therapy, age <8 years, weight <50 kg or >100 kg, intraoperative use of ketamine, or use of major regional block.
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Other: mean ketamine group 58; morphine group 56. Gender (M:F): 17/24. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 3 (ASA 1-3). 3. Type of surgery: Not applicable (not specified).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Ketamine 0.25 mg/kg, the study drug was given as a constant IV infusion over 10 minutes, thus timing to minimise unblinding by bolus administration. IV morphine continued to be administered as needed. they receive a first dose of morphine 4 mg and then 2 mg increments as required. Patients who are ASA=>3, age >65, weight <50 kg, or with any significant congestive cardiac failure, ischaemic heart disease, morbid obesity, renal or hepatic failure are defined as a special population for purposes of the morphine protocol. they receive morphine 2 mg as initial bolus for postoperative pain followed by 1 mg increments. no other analgesics were to be given in the recovery room.. Duration 10 minutes. Concurrent medication/care: n/a. Indirectness: No indirectness (n=22) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Normal Saline, the study drug was given as a constant IV infusion over 10 minutes, thus timing to minimise unblinding by bolus administration. IV morphine continued to be administered as needed. they receive a first dose of morphine 4 mg and then 2 mg increments as required. Patients who are ASA=>3, age >65, weight <50 kg, or with any significant congestive cardiac failure, ischaemic heart disease, morbid obesity, renal or hepatic failure are defined as a special population for purposes of the morphine protocol. they receive morphine 2 mg as initial bolus for postoperative pain followed by 1 mg increments. no other analgesics were to be given in the recovery room.. Duration 10 minutes. Concurrent medication/care: n/a. Indirectness: No indirectness

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at discharge from recovery room. at at discharge.; Group 1: mean 3.79 (SD 1.96); n=19, Group 2: mean 4.23 (SD 2.18); n=22; VRS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: pain score 4 hours after discharge from recovery room. at 4 hors post op; Group 1: mean 3.47 (SD 2.39); n=19, Group 2: mean 3.77 (SD 2.49); n=22; VRS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: rescue analgesia (number of patients) at 24 h post op; Group 1: 5/19, Group 2: 10/22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Additional medication - Morphine consumption at 4 hours at 4 hours post op; Mean; (p: 0.08), Comments: Ketamine + morphine group mean - 8.9 mg, 95% CI 5.6-12.1;
Morphine mean - 14.4, 95% CI 10-18.9;);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Additional medication - Morphine consumption at 24 hours at 24 hours post op; Mean; (p: 0.08), Comments: Ketamine + morphine group mean - 9 mg, 95% CI 3.5-14;
Morphine mean - 14.0, 95% CI 7-18;);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea+vomiting at 24 hours post op; Group 1: 5/19, Group 2: 4/22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital

	readmission

Study	**Arikan 2016[48]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Zekai Tahir Burak Training and Research Hospital, Ankara, Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients belonging to American Society of Anesthesiologist (ASA) physical status I and II, age 30-60 years, scheduled to undergo elective open total abdominal hysterectomy (TAH) for fibroid disease, or uterine myomectomy under general anesthesia were enrolled in the study.
Exclusion criteria	Patients with severe hepatic, renal, cardiovascular impairment, neurological or psychiatric disorders, with allergy to the study drugs, and with history of chronic pain, drug or alcohol abuse. Those with history of current regular use of analgesics, anticonvulsants, antidepressants, or opioids within the last month were excluded from the study.
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Other: 59 years. Gender (M:F): 0/80. Ethnicity: not stated
Further population details	1. Age: <60 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA I and II. 3. Type of surgery: total abdominal hysterectomy.
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients received a bolus dose of ketamine (0.2 mg/kg), and followed by continuous infusion of ketamine (0.05 mg/kg/h). The bolus doses of the study drugs were administered, and their infusions were started simultaneously with the initiation of the IV-PCA morphine.. Concurrent medication/care: n/a. Indirectness: No indirectness (n=22) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Patients received a bolus dose, and continuous infusion of normal saline. The bolus doses of the study drugs were administered, and their

	infusions were started simultaneously with the initiation of the IV-PCA morphine. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: pain score at 6 hours.; Group 1: mean 4 (SD 1.1); n=40, Group 2: mean 4.4 (SD 0.9); n=44; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pain (24 hours post op) - Actual outcome: pain score at 24 hours.; Group 1: mean 2.7 (SD 0.5); n=40, Group 2: mean 3.1 (SD 1.0); n=44; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea at 24 hours post op; Group 1: 5/40, Group 2: 10/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: vomiting at 24 hours post op; Group 1: 1/40, Group 2: 3/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Fiorelli 2015[295]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Naples, Italy
Line of therapy	Not applicable

Duration of study	Intervention + follow up: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Consecutive patients aged more than 18 years old, planned for an elective partial pneumonectomy (partial or total lobectomy involving one or more lobes, except total pneumonectomy) by standard lateral thoracotomy for management of non-small-cell lung cancer.
Exclusion criteria	allergy to ketamine, American Society of Anaesthesiologists' (ASA) classification score more than 3, previous thoracic surgical procedures or lung resection including decortication and/or chest wall resection that may be likely to affect pain threshold, a mental disease that may affect their capacity to express perception of pain, participation to other studies and lack of written informed consent.
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Other: 59.9 years. Gender (M:F): 55/20. Ethnicity: not stated
Further population details	1. Age: <60 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA <3. 3. Type of surgery: elective partial pneumonectomy.
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Five minutes before skin incision, ketamine group received a bolus dose of ketamine 1 mg/kg i.v.. The postoperative analgesia was performed by subcutaneous morphine 10 mg, 30 min before the end of the intervention, i.v. ketorolac 30mg and i.v. paracetamol 1000 mg at the awakening and i.v. patient controlled analgesia (i.v. patient-controlled analgesia [PCA]) which offered a maximum of 1 mg of morphine at 7-min intervals. Concurrent medication/care: n/a. Indirectness: No indirectness (n=37) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. placebo group received an equivalent i.v. volume of normal saline. The postoperative analgesia was performed by subcutaneous morphine 10 mg, 30 min before the end of the intervention, i.v. ketorolac 30mg and i.v. paracetamol 1000 mg at the awakening and i.v. patient controlled analgesia (i.v. patient-controlled analgesia [PCA]) which offered a maximum of 1 mg of morphine at 7-min intervals. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: pain score at 6 hours.; Group 1: mean 4.9 (SD 0.8); n=38, Group 2: mean 5.7 (SD 0.4); n=37; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 2: Pain (24 hours post op) - Actual outcome: pain score at 24 hours.; Group 1: mean 4.1 (SD 0.5); n=38, Group 2: mean 4.8 (SD 0.6); n=37; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 3: Additional opioid consumption (< 6 hours post op) - Actual outcome: Additional opioid consumption at 6 hours.; Group 1: mean 3.7 (SD 0.9); n=38, Group 2: mean 5 (SD 0.3); n=37; Morphine (mg/dL) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 4: Additional opioid consumption (24 hours post op) - Actual outcome: Additional opioid consumption at 24 hours.; Group 1: mean 18 (SD 0.4); n=38, Group 2: mean 22.5 (SD 0.3); n=37; Morphine (mg/dL) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea or vomiting; Group 1: 0/38, Group 2: 0/37 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Hasanein 2011[384]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Egypt
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Morbidly obese patients (ASA physical status II or III), and age between 25 and 50 years, scheduled for elective laparoscopic Roux-en-Y gastric bypass (RYGBP) surgery.
Exclusion criteria	Patients with significant cardiac, respiratory, brain, liver or kidney diseases, or patients having allergy to the study drugs or patients unable to use post-operative PCA.
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Other: 28 years. Gender (M:F): 55/20. Ethnicity: not stated
Further population details	1. Age: 28 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA II or III. 3. Type of surgery: RYGBP.
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. For maintenance of anesthesia, continuous infusion of propofol 6–10 mg/kg/h was started; the rate of propofol was changed to maintain the BIS between 40 and 55. Combined infusion of remifentanil (0.2 lg/kg/min)+ketamine (1 lg/kg/min) were added. Morphine patient controlled analgesia (PCA) was started once the patient pain score recorded 1–2 and continued in the ward for 24 h postoperative. Concurrent medication/care: n/a. Indirectness: No indirectness (n=37) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. For maintenance of anesthesia, continuous infusion of propofol 6–10 mg/kg/h was started; the rate of propofol was changed to maintain the BIS between 40 and 55. Remifentanil infusion in dose of (0.2 lg/kg/min) was added. Morphine patient controlled analgesia (PCA) was started once the patient pain score recorded 1–2 and continued in the ward for 24 h postoperative. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at 6 hours.; Group 1: Median (IQR): 3 (1-2); n=30, Group 2: Median (IQR): 5 (4-8); n=30; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Additional opioid consumption (24 hours post op)

- Actual outcome: Additional opioid consumption at 24 hours.; Group 1: mean 6.1 (SD 40); n=30, Group 2: mean 47.4 (SD 8); n=30; Morphine (mg) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting) - Actual outcome: Nausea at 24 hours post op; Group 1: 2/30, Group 2: 2/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: vomiting at 24 hours post op; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Ilkjaer 1998[427]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Denmark, Department of Urology, Skejby Sygehus, Aarhus University Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients undergoing elective nephrectomy or operation on pelvic structures.
Exclusion criteria	Patients with a history of drug or alcohol abuse, chronic pain or daily intake of analgesics, with contraindications to insertion of epidural catheters, and those unable to cooperate, were not included
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: 50, 55 years. Gender (M:F): 29/23. Ethnicity: not stated
Further population details	1. Age: <60 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA <3. 3. Type of

	surgery: elective partial pneumonectomy.
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. After induction of general anaesthesia, patients received a bolus dose of ketamine 10 mg i.v. before surgical incision, followed by continuous i.v. infusion of ketamine 10 mg h-1 for 48 h after operation. For the first 24 h after surgery, patients received a continuous infusion of 4 ml/h -1 of epidural bupivacaine 2.5 mg ml-1. From 24 to 48 h after operation preceded they received epidural morphine 0.2 mg/h-1. by a bolus dose of 2 mg. In addition, patients were offered PCA with morphine (2.5 mg, lockout time 15 min) for 0–48 h after operation. Concurrent medication/care: n/a. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. After induction of general anaesthesia, patients were allocated randomly to receive a bolus dose of ketamine 10 mg i.v. before surgical incision, followed by continuous i.v. infusion placebo for 48 h after operation. For the first 24 h after surgery, patients received a continuous infusion of 4 ml/h -1 of epidural bupivacaine 2.5 mg ml-1. From 24 to 48 h after operation preceded they received epidural morphine 0.2 mg/h-1. by a bolus dose of 2 mg. In addition, patients were offered PCA with morphine (2.5 mg, lockout time 15 min) for 0–48 h after operation. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO Protocol outcome 1: Pain (24 hours post op) - Actual outcome: pain score at 24 hours.; Group 1: Median (interquartile range) ~5.3 (4.5-6.7); n=24, Group 2: Median (interquartile range) ~4.1 (2.8-5.4); n=28; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Additional opioid consumption (24 hours post op) - Actual outcome: Requiring additional opioid consumption.; Group 1: 9/24 , Group 2: 12/28 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Jendoubi 2017[444]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Tunisia
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients aged ≥18 years and the American Society of Anesthesiologists (ASA) physical Class I or II undergoing elective open nephrectomy.
Exclusion criteria	Known allergy to any of the study medications, an inability to understand the use of patient-controlled analgesia (PCA), renal (serum creatinine >2 mg/dl) or hepatic (alanine aminotransferase or aspartate aminotransferase >2 times normal) dysfunction, a severe cardiovascular disorder (ejection fraction <30%), ASA physical status ≥3, history of chronic pain, epilepsy, psychiatric disorders, chronic use of opioids or alcohol, and drug abuse.
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Other: 48, 56 years. Gender (M:F): 20/20. Ethnicity: not stated
Further population details	1. Age: <60 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA <III. 3. Type of surgery: open nephrectomy.
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Received an IV ketamine bolus of 0.15 mg/kg (0.075 ml/kg of solution of ketamine diluted to a concentration of 2 mg/ml in normal saline) at the induction of anesthesia, followed by infusion of 0.1 mg/kg/h intraoperatively and for 24 h postoperatively. In the PACU, pain was controlled by titration of IV morphine. Concurrent medication/care: n/a. Indirectness: No indirectness (n=37) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. For maintenance of anesthesia, continuous infusion of propofol 6–10 mg/kg/h was started; the rate of propofol was changed to maintain the

	BIS between 40 and 55. Remifentanil infusion in dose of (0.2 lg/kg/min) was added. Morphine patient controlled analgesia (PCA) was started once the patient pain score recorded 1–2 and continued in the ward for 24 h postoperative. In the PACU, pain was controlled by titration of IV morphine. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at 6 hours; Group 1: mean 3.4 (SD 0.8); n=20, Group 2: mean 5.1 (SD 1.2); n=20; VAS 0-10 Top=High is poor outcome. Comment: Values read from a graph
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (24 hours post op)
- Actual outcome: pain score at 24 hours; Group 1: mean 2 (SD 0.5); n=20, Group 2: mean 3.1 (SD 0.8); n=20; VAS 0-10 Top=High is poor outcome. Comment: Values read from a graph
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Additional opioid consumption (24 hours post op)
- Actual outcome: Additional opioid consumption at 24 hours.; Group 1: mean 32 (SD 6.99); n=20, Group 2: mean 47.6 (SD 4.98); n=20; Morphine (mg)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea and vomiting at 24 hours post op; Group 1: 13/20, Group 2: 15/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Psychological effect
- Actual outcome: Dysphoria post op; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Length of hospital stay

- Actual outcome: Length of hospital stay.; Group 1: mean 5.5 days (SD 0.7); n=20, Group 2: mean 7.7 (SD 2.1); n=20; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Functional measure - Actual outcome: Time to mobilisation (h).; Group 1: mean 34 (SD 14); n=20, Group 2: mean 55 (SD 15.7); n=20; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Safavi 2011[1087]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Iran
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	American Society of Anesthesiologists (ASA) physical status I-II patients, aged 18–60 years old, scheduled for open cholecystectomy
Exclusion criteria	Patients with a known history of hypertension, hyperthyroidism, psychiatric disorders, allergy to ketamine, chronic pain syndrome, renal or hepatic insufficiency, history of seizure or intracranial hypertension, or drug or alcohol abuse in the preceding 6 months.
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Other: 48, 54 years. Gender (M:F): 55/20. Ethnicity: not stated
Further population details	1. Age: <60 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA I-II . 3. Type of

	surgery: open cholecystectomy.
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. IV ketamine 1 mg/kg plus subcutaneous infiltration of saline, before surgery. Morphine 0.1 mg/kg was administered for intraoperative analgesia intravenously. Concurrent medication/care: n/a. Indirectness: No indirectness (n=30) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. Subcutaneous infiltration of normal saline 20 mL plus IV saline before surgery. Morphine 0.1 mg/kg was administered for intraoperative analgesia intravenously. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at 6 hours; Group 1: mean 0.2 (SD 0.4); n=30, Group 2: mean 7.4 (SD 1.2); n=30; VAS 0-10 Top=High is poor outcome. Comment: Values read from a graph
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (24 hours post op)
- Actual outcome: pain score at 24 hours; Group 1: mean 0.1 (SD 0.2); n=30, Group 2: mean 6 (SD 2); n=30; VAS 0-10 Top=High is poor outcome. Comment: Values read from a graph
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Additional opioid consumption (24 hours post op)
- Actual outcome: Additional analgesic consumption at 24 hours.; Group 1: mean 23.3 (SD 5.8); n=30, Group 2: mean 151 (SD 52.8); n=30; (mg)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting)
- Actual outcome: Nausea at 24 hours post op; Group 1: 1/30, Group 2: 1/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: vomiting at 24 hours post op; Group 1: 2/30, Group 2: 1/30

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Length of ICU stay - Actual outcome: Length of ICU stay.; Group 1: mean 30.1 minutes (SD 3.4); n=30, Group 2: mean 31.2 (SD 4.1); n=30; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Subramaniam 2011[1207]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	ASA physical status 1, 2, and 3, who underwent lumbar or thoracolumbar laminectomy and fusion for back pain.
Exclusion criteria	Severe cardiopulmonary disease, severe uncontrolled hypertension, raised intracranial pressure, glaucoma, hepato-renal dysfunction, pregnancy, and psychosis
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Other: 57 years. Gender (M:F): 15/15. Ethnicity: not stated
Further population details	1. Age: 57 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA I-III. 3. Type of surgery: lumbar or thoracolumbar laminectomy and fusion.
Indirectness of population	No indirectness

Interventions	(n=15) Intervention 1: Ketamine (IV) and opioid (IV) - Ketamine + opioid. Patients received IV bolus ketamine 0.15 mg/kg at induction and continued on 2 mg/kg/min IV ketamine infusion intraoperatively and postoperatively for 24 hours. IVPCA hydromorphone was started once the patients were awake enough to understand the settings. Concurrent medication/care: n/a. Indirectness: No indirectness (n=15) Intervention 2: Opioid (IV) and placebo - Opioid + placebo. patients received IV normal saline bolus at induction and continued as IV infusion for 24 hours. IVPCA hydromorphone was started once the patients were awake enough to understand the settings. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETAMINE + OPIOID versus OPIOID + PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at 6 hours; Group 1: mean 4.6 (SD 3.6); n=15, Group 2: mean 5.1 (SD 2.8); n=15; VAS 0-10 Top=High is poor outcome.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (24 hours post op)
- Actual outcome: pain score at 24 hours; Group 1: mean 4.7 (SD 2.8); n=15, Group 2: mean 5.3 (SD 3); n=15; VAS 0-10 Top=High is poor outcome.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Additional opioid consumption (<6 hours post op)
- Actual outcome: Additional hydromorphone consumption at <6.; Group 1: mean 3.35 (SD 2.6); n=15, Group 2: mean 2.78 (SD 2.07); n=15; (mg)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Additional opioid consumption (24 hours post op)
- Actual outcome: Additional analgesic consumption at 24 hours.; Group 1: mean 19.36 (SD 13.57); n=15, Group 2: mean 20.72 (SD 17.56); n=15; (mg)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Adverse events (including respiratory depression, nausea, vomiting)

- Actual outcome: Nausea at 24 hours post op; Group 1: 3/15, Group 2: 7/15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: vomiting at 24 hours post op; Group 1: 0/15, Group 2: 1/15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Length of hospital stay - Actual outcome: Length of hospital stay.; Group 1: mean 6.73 days (SD 5.23); n=15, Group 2: mean 4.8 (SD 1.82); n=15; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 7: Length of ICU stay - Actual outcome: Length of ICU stay.; Group 1: mean 233.4 minutes (SD 175.38); n=15, Group 2: mean 209.33 (SD 70.02); n=15; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 8: Functional measure - Actual outcome: Mobilised at 48 hours post op; Group 1: 7/15, Group 2: 9/15 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Hospital readmission

Study	Singh 2013[1157]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in India; Setting: n/a
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	80 adult patients of either gender belonging to ASA grades 1 and 2 and scheduled for laparoscopic cholecystectomy using a standardized general anesthesia technique

Appendix D: Forest plots

D.1 IV opioid plus ketamine versus IV opioid

Figure 125: Pain: VAS < 6hours

Study or Subgroup	Opiod + Ketamine Mean	SD	Total	Opioid Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akhavanakbari 2014	3.175	0.601	40	5.1	0.7	20	4.3%	-1.92 [-2.28, -1.57]
Arikan 2016	4	1.1	40	4.4	0.9	40	4.3%	-0.40 [-0.84, 0.04]
Cengiz 2014	0.9	0.66	30	2.1	0.8	30	4.3%	-1.20 [-1.57, -0.83]
D'alonzo 2011	3.8	2.1	20	3.1	2.8	20	3.5%	0.70 [-0.83, 2.23]
Dahi-Taleghani 2014	1.5	0.8	70	2.2	1.1	70	4.3%	-0.70 [-1.02, -0.38]
Dahl 2000	3.6	1.4	60	4.1	1.6	29	4.2%	-0.50 [-1.18, 0.18]
Fiorelli 2015	4.9	0.8	38	5.7	0.4	37	4.3%	-0.80 [-1.09, -0.51]
Gillies 2007	3.47	2.39	19	3.77	2.49	22	3.5%	-0.30 [-1.80, 1.20]
Haliloglu 2016	1.23	0.91	26	1.07	0.97	26	4.2%	0.16 [-0.35, 0.67]
Jendoubi 2017	3.4	0.8	20	5.1	1.2	20	4.2%	-1.70 [-2.33, -1.07]
Kim 2013	6.3	2.34	35	6.8	1.85	17	3.8%	-0.50 [-1.67, 0.67]
Lak 2010	4.56	1.66	20	8	1.26	20	4.0%	-3.44 [-4.35, -2.53]
Launo 2004	2.95	1.28	20	2.6	1.01	20	4.1%	0.35 [-0.36, 1.06]
Leal 2013	0.9	1.2	20	0.5	0.9	20	4.2%	0.40 [-0.26, 1.06]
Leal 2015	0.9	1.2	28	0.7	1	28	4.2%	0.20 [-0.38, 0.78]
Moro 2017	3.23	2.936	80	3.2	2.8	39	3.9%	0.03 [-1.06, 1.12]
Morue 2018	1.8	2.3	61	2.3	2.4	60	4.1%	-0.50 [-1.34, 0.34]
Nesher 2009	3.7	0.7	21	5.6	1	20	4.2%	-1.90 [-2.43, -1.37]
Ong 2001	2.1	2.05	20	3.1	2.19	20	3.7%	-1.00 [-2.31, 0.31]
Safavi 2011	0.2	0.4	30	7.4	1.4	30	4.2%	-7.20 [-7.72, -6.68]
Snijdelaar 2004	1.4	1.2	13	2.9	1.6	12	3.9%	-1.50 [-2.62, -0.38]
Song 2013	3.7	2.3	24	3.8	2.1	25	3.8%	-0.10 [-1.33, 1.13]
Song 2014	5.36	1.24	25	5.905	1.678	50	4.2%	-0.54 [-1.22, 0.13]
Subramaniam 2011	4.6	3.6	15	5.1	2.8	15	2.8%	-0.50 [-2.81, 1.81]
Yeom 2012	5.1	2	20	8.2	1.5	20	3.9%	-3.10 [-4.20, -2.00]
Total (95% CI)			**795**			**710**	**100.0%**	**-1.06 [-1.72, -0.41]**

Heterogeneity: Tau² = 2.60; Chi² = 716.59, df = 24 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.17 (P = 0.002)

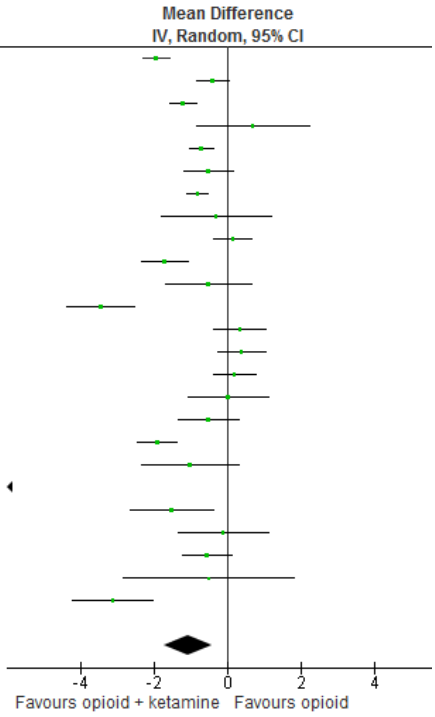
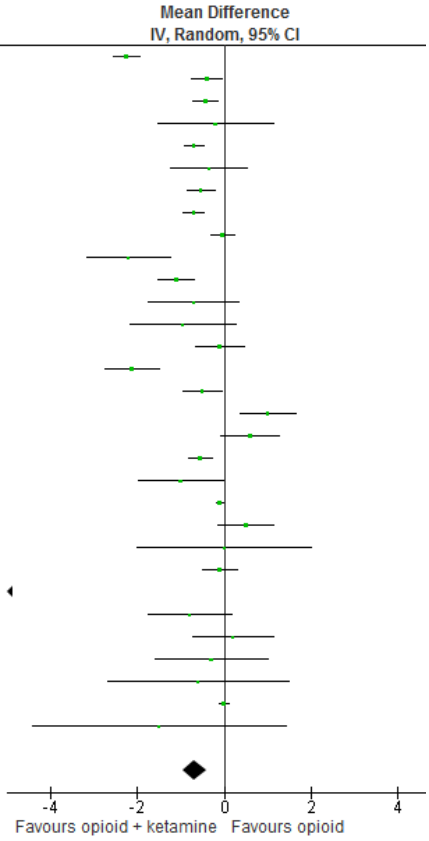


Figure 126: Pain VAS 6 - 24 hours

Study or Subgroup	Opiod + Ketamine Mean	SD	Total	Opioid Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akhavanakbari 2014	1.75	0.444	40	4	0.64	20	4.0%	-2.25 [-2.56, -1.94]
Arikan 2016	2.7	0.5	40	3.1	1	40	4.0%	-0.40 [-0.75, -0.05]
Cengiz 2014	0.2	0.48	30	0.63	0.61	30	4.1%	-0.43 [-0.71, -0.15]
D'alonzo 2011	2.6	2.2	20	2.8	2.1	20	2.1%	-0.20 [-1.53, 1.13]
Dahi-Taleghani 2014	1	0.5	70	1.7	0.8	70	4.1%	-0.70 [-0.92, -0.48]
Dahl 2000	5.45	2.2	60	5.8	1.9	29	2.9%	-0.35 [-1.24, 0.54]
Deng 2009	1.467	0.899	150	2	1	50	4.0%	-0.53 [-0.85, -0.22]
Fiorelli 2015	4.1	0.5	38	4.8	0.6	37	4.1%	-0.70 [-0.95, -0.45]
Haliloglu 2016	0.42	0.5	26	0.46	0.51	26	4.1%	-0.04 [-0.31, 0.23]
Javery 1996	2.3	1.67	22	4.5	1.54	20	2.8%	-2.20 [-3.17, -1.23]
Jendoubi 2017	2	0.5	20	3.1	0.8	20	3.9%	-1.10 [-1.51, -0.69]
Joly 2005	3.6	2	23	4.3	2.365	50	2.6%	-0.70 [-1.75, 0.35]
Kim 2013	3.64	1.63	35	4.6	2.3	17	2.3%	-0.96 [-2.18, 0.26]
Lahtinen 2004	3.3	1.3266	44	3.4	1.3565	46	3.6%	-0.10 [-0.65, 0.45]
Lak 2010	2.48	1.04	20	4.6	0.96	20	3.5%	-2.12 [-2.74, -1.50]
Launo 2004	0.9	0.51	20	1.4	0.89	20	3.8%	-0.50 [-0.95, -0.05]
Leal 2013	1.5	1.3	20	0.5	0.7	20	3.4%	1.00 [0.35, 1.65]
Leal 2015	1.4	1.5	28	0.8	1	28	3.4%	0.60 [-0.07, 1.27]
Menigaux 2000	2.35	0.512	30	2.9	0.4	15	4.1%	-0.55 [-0.82, -0.28]
Michelet 2007	3	1.4	24	4	2	24	2.8%	-1.00 [-1.98, -0.02]
Moro 2017	3.8	0.2327	80	3.9	0.21	39	4.2%	-0.10 [-0.18, -0.02]
Morue 2018	1.7	2.1	61	1.2	1.5	60	3.4%	0.50 [-0.15, 1.15]
Perrin 2009	2.2	1.7	5	2.2	1.8	7	1.3%	0.00 [-2.00, 2.00]
Remerand 2009	1.4	1.4	79	1.5	1.2	75	3.9%	-0.10 [-0.51, 0.31]
Safavi 2011	0.1	0.2	30	6	2	30	3.3%	-5.90 [-6.62, -5.18]
Snijdelaar 2004	1.2	1	13	2	1.4	12	2.8%	-0.80 [-1.76, 0.16]
Song 2013	2.5	1.8	24	2.3	1.5	25	2.9%	0.20 [-0.73, 1.13]
Song 2013	3.2	2	24	3.5	2.6	25	2.2%	-0.30 [-1.60, 1.00]
Subramaniam 2011	4.7	2.8	15	5.3	3	15	1.2%	-0.60 [-2.68, 1.48]
Sveticic 2008	0.77	0.56	176	0.77	0.42	176	4.2%	0.00 [-0.10, 0.10]
Yeom 2012	3.6	2	2	5.1	2.1	20	0.7%	-1.50 [-4.42, 1.42]
Total (95% CI)			**1269**			**1086**	**100.0%**	**-0.68 [-0.96, -0.41]**

Heterogeneity: Tau² = 0.46; Chi² = 568.63, df = 30 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.86 (P < 0.00001)

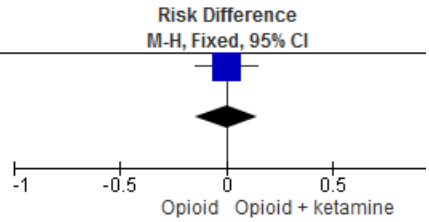


1

Figure 127: Pain None at 4 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Edwards 1993	0	24	0	9	100.0%	0.00 [-0.15, 0.15]
Total (95% CI)		**24**		**9**	**100.0%**	**0.00 [-0.15, 0.15]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

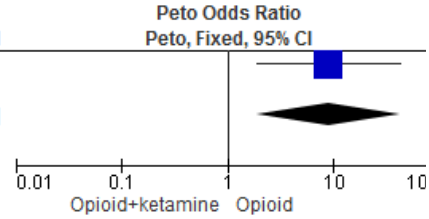


2

Figure 128: Pain Mild at 4 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Edwards 1993	13	24	0	9	100.0%	9.03 [1.93, 42.26]
Total (95% CI)		**24**		**9**	**100.0%**	**9.03 [1.93, 42.26]**
Total events	13		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.79 (P = 0.005)



3

Figure 129: Pain Moderate at 4 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edwards 1993	10	24	5	9	100.0%	0.75 [0.35, 1.59]
Total (95% CI)		**24**		**9**	**100.0%**	**0.75 [0.35, 1.59]**
Total events	10		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)

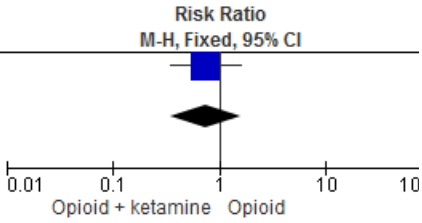


Figure 130: Pain Severe at 4 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edwards 1993	6	24	4	9	100.0%	0.56 [0.21, 1.54]
Total (95% CI)		**24**		**9**	**100.0%**	**0.56 [0.21, 1.54]**
Total events	6		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)

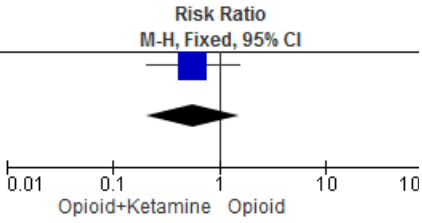


Figure 131: Pain Very severe at 4 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edwards 1993	1	24	1	9	100.0%	0.38 [0.03, 5.38]
Total (95% CI)		**24**		**9**	**100.0%**	**0.37 [0.03, 5.38]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

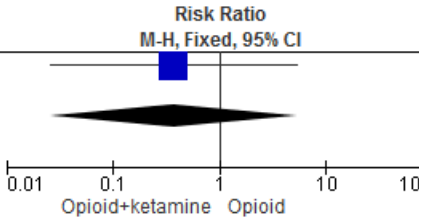


Figure 132: Pain None at 24 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edwards 1993	11	24	2	9	100.0%	2.06 [0.56, 7.55]
Lo 2008	0	15	0	15		Not estimable
Total (95% CI)		**39**		**24**	**100.0%**	**2.06 [0.56, 7.55]**
Total events	11		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.27)

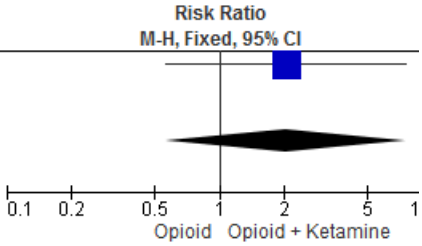


Figure 133: Pain Mild at 24 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edwards 1993	10	24	3	9	32.7%	1.25 [0.44, 3.53]
Lo 2008	7	15	9	15	67.3%	0.78 [0.39, 1.54]
Total (95% CI)		**39**		**24**	**100.0%**	**0.93 [0.52, 1.65]**
Total events	17		12			

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

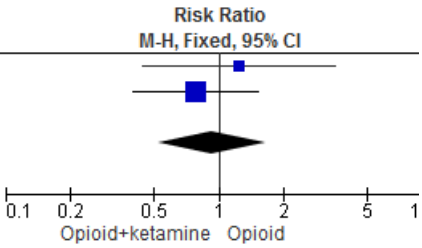
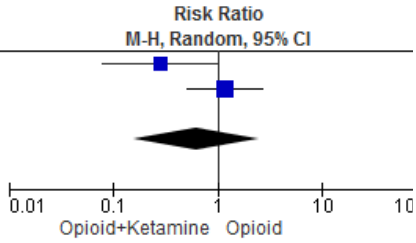


Figure 134: Pain Moderate at 24 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Edwards 1993	3	24	4	9	43.8%	0.28 [0.08, 1.02]
Lo 2008	7	15	6	15	56.2%	1.17 [0.51, 2.66]
Total (95% CI)		**39**		**24**	**100.0%**	**0.63 [0.16, 2.51]**
Total events	10		10			

Heterogeneity: Tau² = 0.72; Chi² = 3.36, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.66 (P = 0.51)

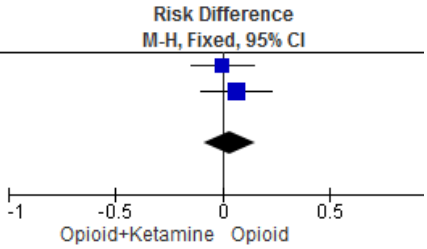


1

Figure 135: Severe at 24 hours

Study or Subgroup	Opioid+Ketamine Events	Total	Opioid Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Edwards 1993	0	24	0	9	46.6%	0.00 [-0.15, 0.15]
Lo 2008	1	15	0	15	53.4%	0.07 [-0.10, 0.23]
Total (95% CI)		**39**		**24**	**100.0%**	**0.04 [-0.08, 0.16]**
Total events	1		0			

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)

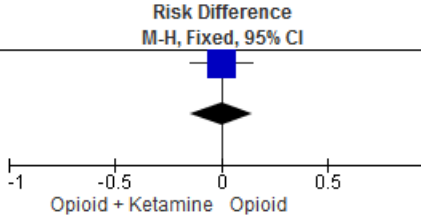


2

Figure 136: Pain Very severe at 24 hours

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Edwards 1993	0	24	0	9	100.0%	0.00 [-0.15, 0.15]
Total (95% CI)		**24**		**9**	**100.0%**	**0.00 [-0.15, 0.15]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

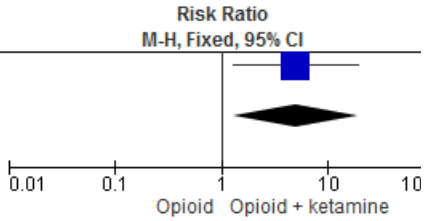


3

Figure 137: Patients with no pain

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hadi 2010	10	15	2	15	100.0%	5.00 [1.31, 19.07]
Total (95% CI)		**15**		**15**	**100.0%**	**5.00 [1.31, 19.07]**
Total events	10		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.36 (P = 0.02)

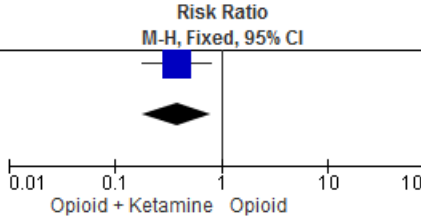


4

Figure 138: Patients with pain

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hadi 2010	5	15	13	15	100.0%	0.38 [0.18, 0.81]
Total (95% CI)		**15**		**15**	**100.0%**	**0.38 [0.18, 0.81]**
Total events	5		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.52 (P = 0.01)

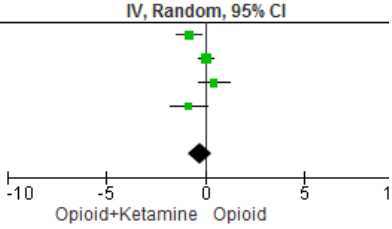


5

Figure 139: Adverse events - mean nausea score 0 - 24 hours

Study or Subgroup	Opiod + Ketamine Mean	SD	Total	Opioid Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Javery 1996	1.39	0.755	22	2.2	1.196	20	26.1%	-0.80 [-1.44, -0.17]
Moro 2017	14.23	35.43	80	12	30.8	39	32.6%	0.07 [-0.32, 0.45]
Snijdelaar 2004	1.1	2.1	13	0.4	0.6	12	22.0%	0.43 [-0.36, 1.23]
Stubhaug 1997	0.2	0.4	10	0.8	0.9	10	19.3%	-0.83 [-1.75, 0.10]
Total (95% CI)			**125**			**81**	**100.0%**	**-0.25 [-0.83, 0.32]**

Heterogeneity: Tau² = 0.23; Chi² = 9.43, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 0.86 (P = 0.39)

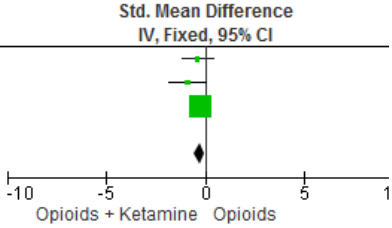


1

Figure 140: Adverse events - mean nausea score 24 - 48 hours

Study or Subgroup	Opiod + Ketamine Mean	SD	Total	Opioid Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Snijdelaar 2004	0.1	0.4	13	0.4	1	12	11.1%	-0.39 [-1.18, 0.41]
Stubhaug 1997	0.1	0.3	10	0.6	0.7	10	8.1%	-0.89 [-1.82, 0.04]
Yamauchi 2008	1.161	1.241	133	1.5	1.959	67	80.8%	-0.22 [-0.52, 0.07]
Total (95% CI)			**156**			**89**	**100.0%**	**-0.29 [-0.56, -0.03]**

Heterogeneity: Chi² = 1.86, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.18 (P = 0.03)

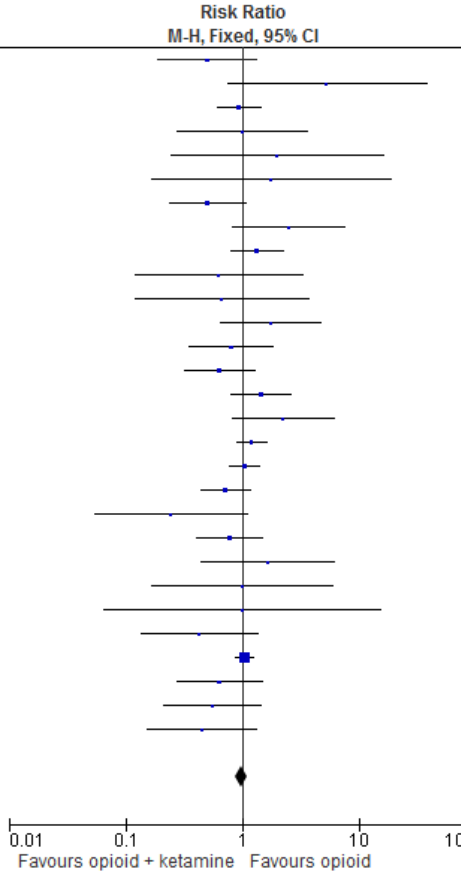


2

Figure 141: Adverse events – Nausea

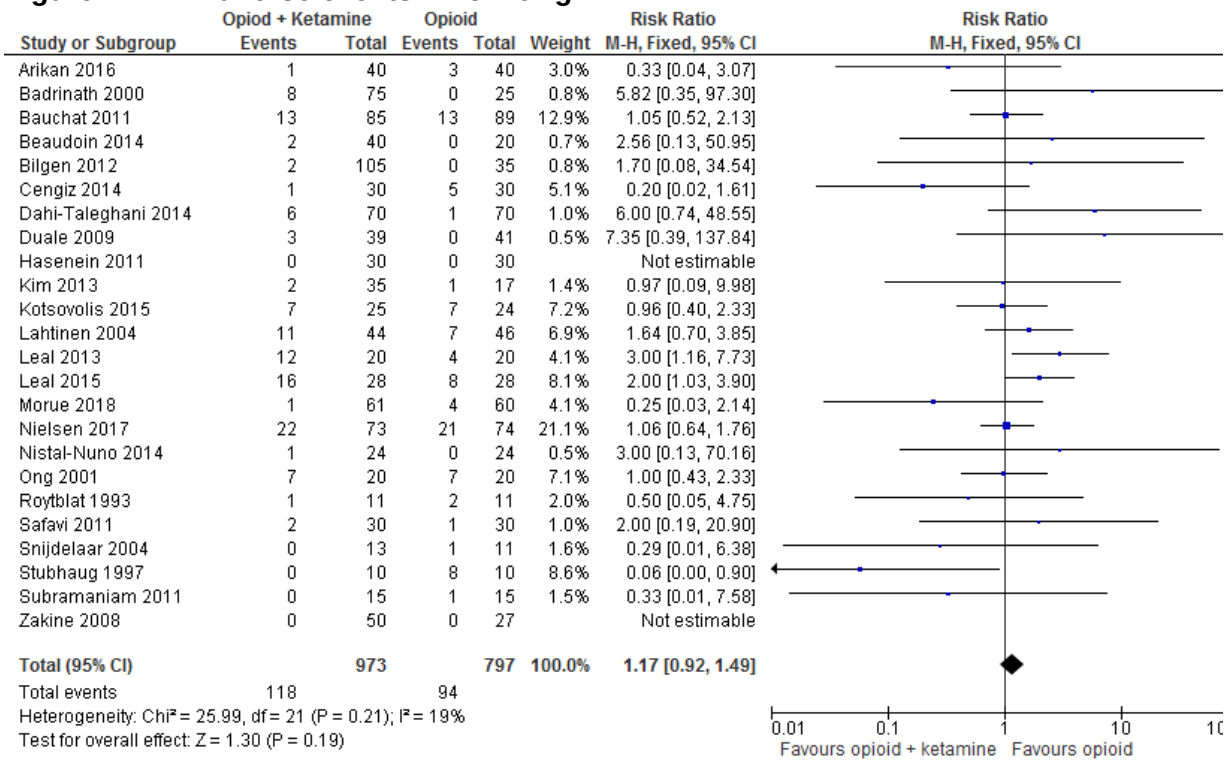
Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arikan 2016	5	40	10	40	2.9%	0.50 [0.19, 1.33]
Badrinath 2000	16	75	1	25	0.4%	5.33 [0.74, 38.20]
Bauchat 2011	27	85	30	89	8.5%	0.94 [0.62, 1.44]
Beaudoin 2014	6	40	3	20	1.2%	1.00 [0.28, 3.59]
Bilgen 2012	6	105	1	35	0.4%	2.00 [0.25, 16.04]
Burstal 2001	2	37	1	33	0.3%	1.78 [0.17, 18.78]
Cengiz 2014	7	30	14	30	4.0%	0.50 [0.24, 1.06]
Dahi-Taleghani 2014	10	70	4	70	1.2%	2.50 [0.82, 7.59]
Duale 2009	19	39	15	41	4.2%	1.33 [0.79, 2.23]
Guillou 2003	2	41	4	52	1.0%	0.63 [0.12, 3.29]
Hasenein 2011	2	30	3	30	0.9%	0.67 [0.12, 3.71]
Jaksch 2002	7	15	4	15	1.2%	1.75 [0.64, 4.75]
Kim 2013	10	35	6	17	2.3%	0.81 [0.35, 1.86]
Kotsovolis 2015	8	25	12	24	3.5%	0.64 [0.32, 1.29]
Lahtinen 2004	18	44	13	46	3.7%	1.45 [0.81, 2.59]
Launo 2004	9	20	4	20	1.2%	2.25 [0.83, 6.13]
Leal 2013	18	20	15	20	4.3%	1.20 [0.90, 1.61]
Leal 2015	22	28	21	28	6.1%	1.05 [0.79, 1.40]
McKay 2007	10	19	16	22	4.3%	0.72 [0.44, 1.19]
Morue 2018	2	61	8	60	2.3%	0.25 [0.05, 1.11]
Nielsen 2017	13	73	17	74	4.9%	0.78 [0.41, 1.48]
Nistal-Nuno 2014	5	24	3	24	0.9%	1.67 [0.45, 6.21]
Roytblat 1993	2	11	2	11	0.6%	1.00 [0.17, 5.89]
Safavi 2011	1	30	1	30	0.3%	1.00 [0.07, 15.26]
Subramaniam 2011	3	15	7	15	2.0%	0.43 [0.14, 1.35]
Sveticic 2008	109	176	104	176	30.0%	1.05 [0.89, 1.24]
Unlugenc 2002	6	22	9	21	2.7%	0.64 [0.27, 1.48]
Unlugenc 2003	5	29	9	29	2.6%	0.56 [0.21, 1.46]
Zakine 2008	5	50	6	27	2.2%	0.45 [0.15, 1.34]
Total (95% CI)		**1289**		**1124**	**100.0%**	**0.98 [0.88, 1.10]**
Total events	355		343			

Heterogeneity: Chi² = 35.07, df = 28 (P = 0.17); I² = 20%
Test for overall effect: Z = 0.36 (P = 0.72)



3

Figure 142: Adverse events – Vomiting



1

Figure 143: Adverse events – Nausea and Vomiting

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Adam 2005	2	20	3	20	1.1%	0.67 [0.12, 3.57]
Aubrun 2008	23	45	23	45	8.5%	1.00 [0.67, 1.50]
Aveline 2006	6	23	10	23	3.7%	0.60 [0.26, 1.38]
Aveline 2009	4	25	9	23	3.5%	0.41 [0.15, 1.15]
Ayoglu 2005	6	20	8	20	3.0%	0.75 [0.32, 1.77]
Chazan 2010	10	24	15	22	5.8%	0.61 [0.35, 1.06]
Darwish 2005	4	30	6	30	2.2%	0.67 [0.21, 2.13]
Fiorelli 2015	0	38	0	37		Not estimable
Ganne 2005	5	30	3	31	1.1%	1.72 [0.45, 6.58]
Garg 2016	3	22	1	22	0.4%	3.00 [0.34, 26.66]
Gillies 2007	5	19	4	22	1.4%	1.45 [0.45, 4.63]
Guignard 2002	4	25	5	25	1.9%	0.80 [0.24, 2.64]
Haliloglu 2016	4	26	5	26	1.9%	0.80 [0.24, 2.65]
Hong 2011	3	20	2	20	0.7%	1.50 [0.28, 8.04]
Jendoubi 2017	13	20	15	20	5.6%	0.87 [0.58, 1.30]
Joly 2005	7	23	15	50	3.5%	1.01 [0.48, 2.15]
Kapfer 2005	8	22	4	21	1.5%	1.91 [0.67, 5.40]
Kollender 2008	6	28	12	29	4.4%	0.52 [0.23, 1.19]
Lak 2010	3	20	3	20	1.1%	1.00 [0.23, 4.37]
Li 2016	1	17	6	15	2.4%	0.15 [0.02, 1.09]
Lo 2008	8	15	10	15	3.7%	0.80 [0.44, 1.45]
Michelet 2007	6	24	7	24	2.6%	0.86 [0.34, 2.18]
Nesher 2008	11	28	17	29	6.2%	0.67 [0.39, 1.16]
Nesher 2009	1	21	3	20	1.1%	0.32 [0.04, 2.80]
Parikh 2011	0	30	4	30	1.7%	0.11 [0.01, 1.98]
Reza 2010	6	30	8	30	3.0%	0.75 [0.30, 1.90]
Singh 2013	11	60	3	20	1.7%	1.22 [0.38, 3.95]
Song 2013	17	25	14	25	5.2%	1.21 [0.78, 1.88]
Suzuki 1999	28	105	9	35	5.0%	1.04 [0.54, 1.98]
Tang 2010	3	40	3	40	1.1%	1.00 [0.21, 4.66]
Weinbroum 2003	9	131	30	114	11.9%	0.26 [0.13, 0.53]
Yeom 2012	5	20	9	20	3.3%	0.56 [0.23, 1.37]
Total (95% CI)		**1026**		**923**	**100.0%**	**0.76 [0.66, 0.88]**
Total events	222		266			

Heterogeneity: Chi² = 34.47, df = 30 (P = 0.26); I² = 13%
Test for overall effect: Z = 3.67 (P = 0.0002)

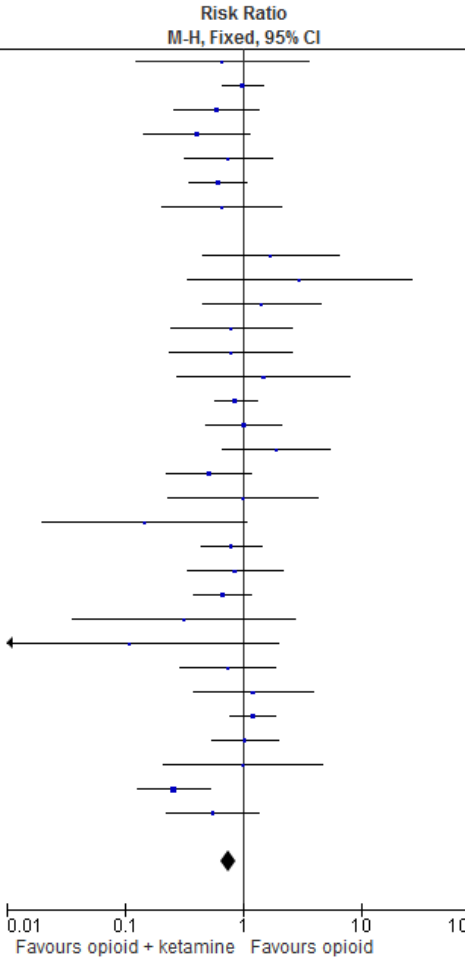


Figure 144: Adverse events – Respiratory depression

Study or Subgroup	Opiod + Ketamine Events	Total	Opioid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aubrun 2008	7	45	5	45	9.3%	1.40 [0.48, 4.08]
Edwards 1993	1	30	3	30	5.6%	0.33 [0.04, 3.03]
Launo 2004	0	20	1	20	2.8%	0.33 [0.01, 7.72]
Morue 2018	29	61	35	60	65.6%	0.81 [0.58, 1.14]
Parikh 2011	0	30	0	30		Not estimable
Sveticic 2008	19	176	9	176	16.7%	2.11 [0.98, 4.54]
Total (95% CI)		**362**		**361**	**100.0%**	**1.05 [0.77, 1.42]**
Total events	56		53			

Heterogeneity: Chi² = 7.14, df = 4 (P = 0.13); I² = 44%
Test for overall effect: Z = 0.29 (P = 0.77)

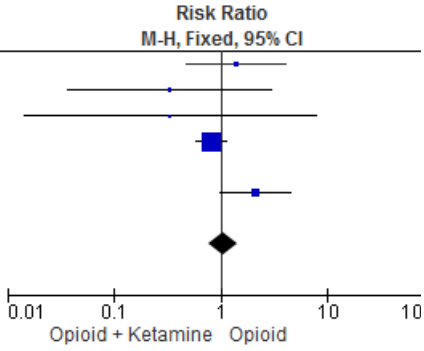
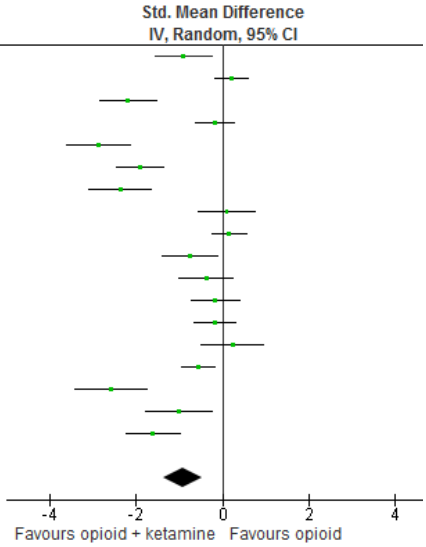


Figure 145: Additional opioid consumption < 6 hours

Study or Subgroup	Opiod + Ketamine Mean	SD	Total	Opioid Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ayoglu 2005	5	3.1305	20	8.1	3.5777	20	5.5%	-0.90 [-1.56, -0.25]
Bilgen 2012	23.67	7.782	105	22	7	35	5.9%	0.22 [-0.16, 0.60]
Cengiz 2014	28.73	11.88	30	55.76	12.56	30	5.5%	-2.18 [-2.83, -1.53]
Dahl 2000	13.94	6.79	60	15.1	6.5	29	5.8%	-0.17 [-0.62, 0.27]
Darwish 2005	9.2	1.1	30	12	0.8	30	5.3%	-2.87 [-3.61, -2.14]
Fiorelli 2015	3.7	0.9	38	5	0.3	37	5.7%	-1.91 [-2.46, -1.36]
Haliloglu 2016	11.3	2.1	26	16.7	2.4	26	5.3%	-2.36 [-3.08, -1.64]
Han 2013	189	63.1	19	183	48.7	17	5.5%	0.10 [-0.55, 0.76]
Katz 2004	22.1	8.3	50	20.9	7.6	46	5.9%	0.15 [-0.25, 0.55]
Lee 2014	39	38	20	67.5	37.5	20	5.5%	-0.74 [-1.38, -0.10]
Ong 2001	60	37.9	20	86.1	89.3	20	5.5%	-0.37 [-1.00, 0.25]
Song 2013	143	58	24	156	90	25	5.6%	-0.17 [-0.73, 0.39]
Song 2014	25.2	7.1	25	26.4	6.54	50	5.8%	-0.18 [-0.66, 0.30]
Subramaniam 2011	3.35	2.6	15	2.78	2.07	15	5.3%	0.24 [-0.48, 0.95]
Suzuki 1999	97	82	105	145	93	35	5.9%	-0.56 [-0.95, -0.17]
Unlugenc 2002	280	44	22	405	51	21	5.1%	-2.58 [-3.41, -1.75]
Wilder-Smith 1998	14.9	2.7	15	16.9	0.3	15	5.2%	-1.01 [-1.78, -0.25]
Yalcin 2012	23.53	8.96	26	36.7	7.16	27	5.5%	-1.60 [-2.23, -0.98]
Total (95% CI)			**650**			**498**	**100.0%**	**-0.91 [-1.35, -0.47]**

Heterogeneity: Tau² = 0.81; Chi² = 187.65, df = 17 (P < 0.00001); I² = 91%
Test for overall effect: Z = 4.07 (P < 0.0001)

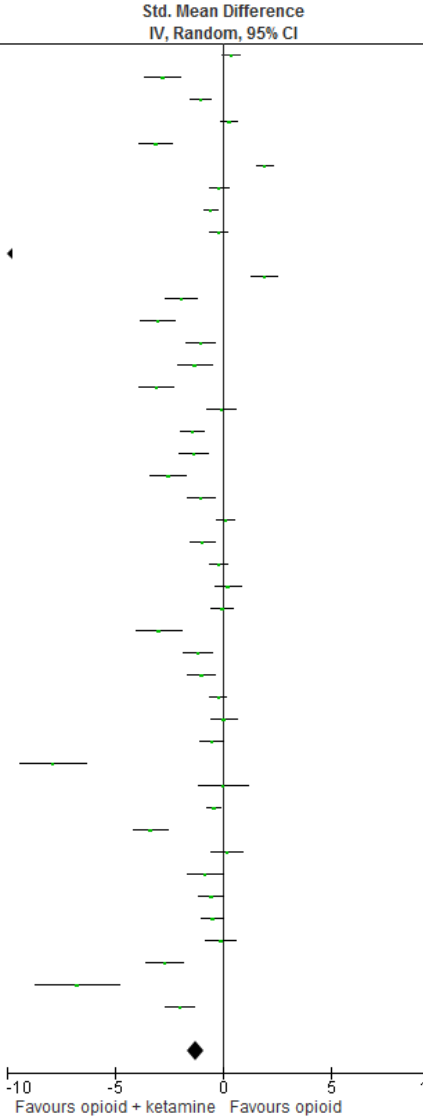


1

Figure 146: Additional opioid consumption 6-24 hours

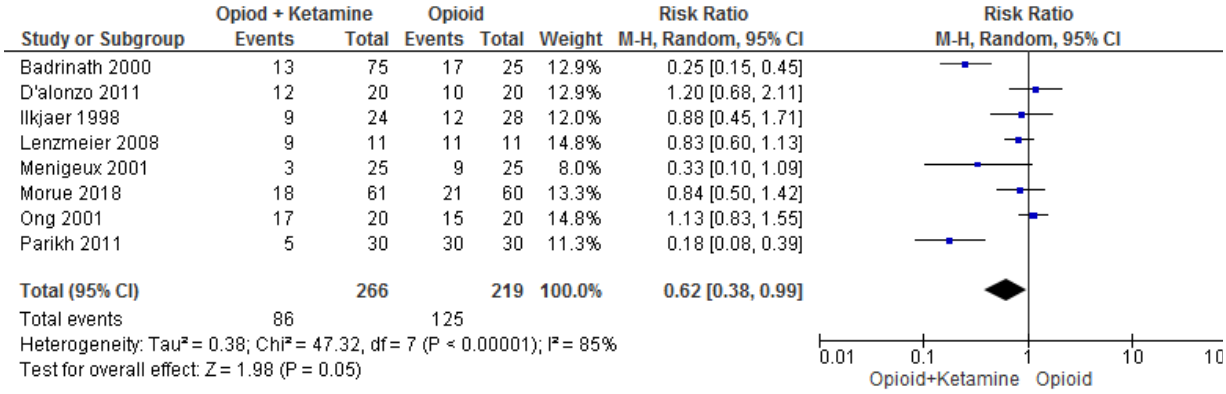
Study or Subgroup	Opiod + Ketamine Mean	SD	Total	Opioid Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Aubrun 2008	24.8	19.2	45	17.8	16.4	45	2.4%	0.39 [-0.03, 0.81]
Aveline 2009	39.2	6.5	25	56.8	5.9	23	2.2%	-2.78 [-3.59, -1.97]
Badrinath 2000	0.9767	2.367	75	3.6	3.2	25	2.4%	-1.00 [-1.48, -0.53]
Bilgen 2012	43	16.58	105	38	14	35	2.4%	0.31 [-0.07, 0.70]
Cengiz 2014	47	15.3	30	85.2	8.01	30	2.3%	-3.09 [-3.85, -2.32]
Dahi-Taleghani 2014	12	3	70	7	2	70	2.4%	1.95 [1.55, 2.35]
Dahl 2000	19.2	6.4	60	20.4	8	29	2.4%	-0.17 [-0.62, 0.27]
Deng 2009	1,572	468.5	150	1,838	523	50	2.4%	-0.55 [-0.87, -0.22]
Dullenkopf 2009	8.766	9.035	77	10.3	6.8	33	2.4%	-0.18 [-0.59, 0.23]
Fiorelli 2015	18	0.4	38	22.5	0.3	37	1.4%	-12.57 [-14.69, -10.46]
Ganne 2005	33.3	14.9	30	3.9	15.3	31	2.3%	1.92 [1.31, 2.53]
Garg 2016	2.45	2.067	22	15.64	9.31	22	2.3%	-1.92 [-2.65, -1.20]
Ghazi-Saidi K 2002	6.25	3.42	27	17.73	4.08	26	2.2%	-3.01 [-3.81, -2.21]
Hadi 2009	45	5	20	60	20	20	2.3%	-1.01 [-1.67, -0.35]
Hadi 2010	45	5	15	60	15	15	2.2%	-1.31 [-2.10, -0.51]
Haliloglu 2016	25	3.7	26	36.4	3.6	26	2.2%	-3.08 [-3.90, -2.26]
Han 2013	602	113.8	19	608.2	83.7	17	2.3%	-0.06 [-0.71, 0.59]
Hasenein 2011	6.1	40	30	47.4	8	30	2.4%	-1.41 [-1.98, -0.84]
Javery 1996	25.82	16.4	22	51.1	20.8	20	2.3%	-1.33 [-2.01, -0.66]
Jendoubi 2017	32	6.99	20	47.6	4.98	20	2.2%	-2.52 [-3.37, -1.67]
Kapfer 2005	9	5	22	17	10	21	2.3%	-1.00 [-1.64, -0.36]
Katz 2004	33.2	14	50	31.4	13.5	46	2.4%	0.13 [-0.27, 0.53]
Kollender 2008	14.6	11.4	28	32.9	24.9	29	2.4%	-0.93 [-1.47, -0.38]
Kwok 2004	2.9	3.1	45	3.4	2.7	45	2.4%	-0.17 [-0.58, 0.24]
Leal 2013	29	18.4	20	25.1	13.3	20	2.3%	0.24 [-0.38, 0.86]
Leal 2015	27.4	18.3	28	27.7	12.9	28	2.4%	-0.02 [-0.54, 0.51]
Li 2016	25.13	2.9	17	33.4	2.5	15	2.1%	-2.96 [-4.00, -1.92]
Menigaux 2000	26.2	18.21	30	49.7	24.1	15	2.3%	-1.14 [-1.80, -0.47]
Miziara 2016	5.2	2.707	21	7.525	1.872	21	2.3%	-0.98 [-1.62, -0.34]
Moro 2017	1.2	1.947	80	1.6	2.2	39	2.4%	-0.20 [-0.58, 0.19]
Murdoch 2002	67.6	25.1	21	66.4	17.7	21	2.3%	0.05 [-0.55, 0.66]
Nesher 2008	1	1.4	28	2	2.3	29	2.4%	-0.52 [-1.04, 0.01]
Parikh 2011	5.8	1.48	30	18.1	1.6	30	1.8%	-7.88 [-9.42, -6.33]
Perrin 2009	39.4	36.5	5	39	42.2	7	2.0%	0.01 [-1.14, 1.16]
Remerand 2009	14	13	79	19	12	75	2.4%	-0.40 [-0.72, -0.08]
Safavi 2011	23.3	5.8	30	151	52.8	30	2.2%	-3.36 [-4.16, -2.55]
Sahin 2004	20.28	11.81	17	17.93	12.02	14	2.3%	0.19 [-0.52, 0.90]
Snijdelaar 2004	47.9	26.2	13	73.4	34.8	12	2.2%	-0.81 [-1.63, 0.02]
Song 2013	399	147	24	504	232	25	2.4%	-0.53 [-1.10, 0.04]
Song 2014	58.1	1.9	25	59.3	2.737	50	2.4%	-0.48 [-0.96, 0.01]
Subramaniam 2011	19.36	13.57	15	20.72	17.56	15	2.3%	-0.08 [-0.80, 0.63]
Unlugenc 2002	850	56	22	975	31	21	2.2%	-2.69 [-3.54, -1.85]
Wilder-Smith 1998	0	12.4	15	60.9	0.9	15	1.5%	-6.74 [-8.70, -4.78]
Yalcin 2012	35.34	13.71	26	73.03	22.41	27	2.3%	-1.99 [-2.66, -1.32]
Total (95% CI)			**1597**			**1254**	**100.0%**	**-1.25 [-1.63, -0.86]**

Heterogeneity: Tau² = 1.59; Chi² = 864.05, df = 43 (P < 0.00001); I² = 95%
Test for overall effect: Z = 6.27 (P < 0.00001)



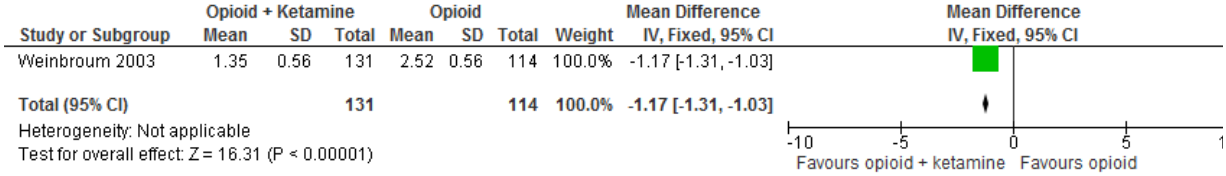
1

Figure 147: Requiring additional opioid 24 hours



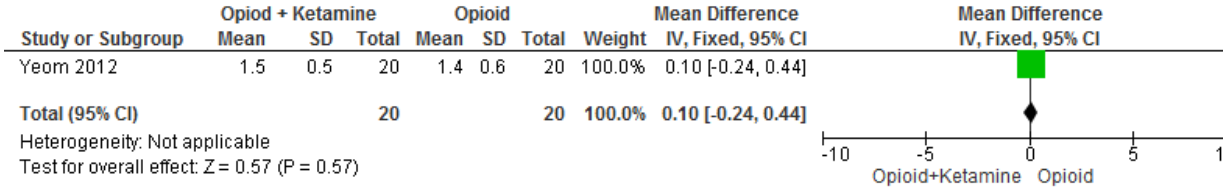
2

Figure 148: Morphine Injections (per patient)



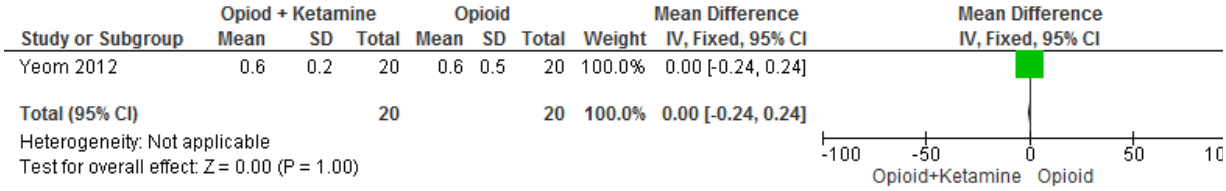
3

Figure 149: PCA Fentanyl infusion rate <6 hours



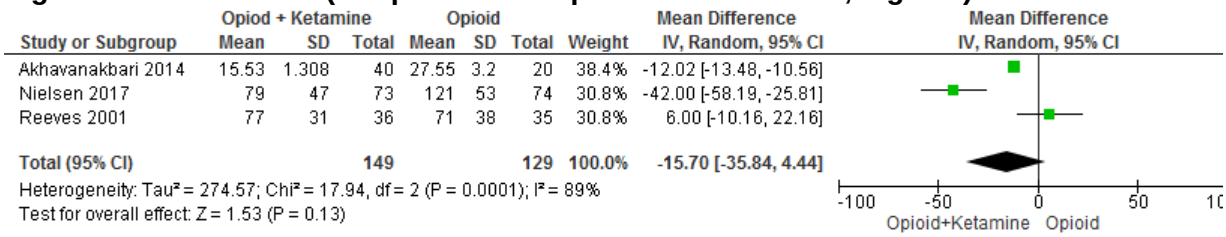
4

Figure 150: PCA Fentanyl infusion rate <24 hours



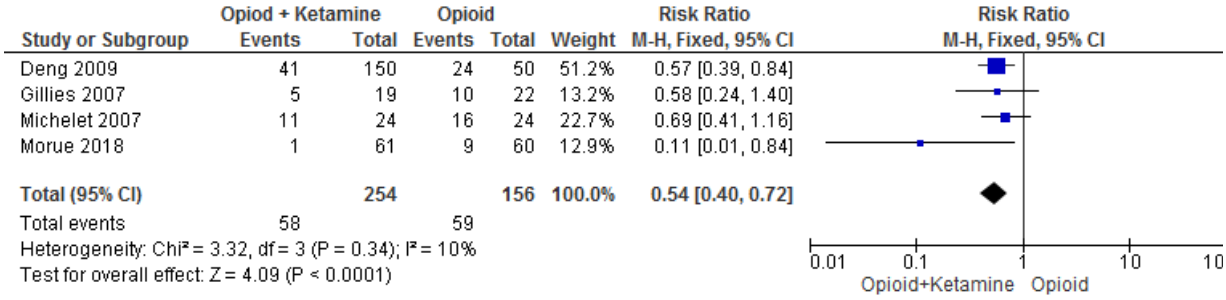
5

Figure 151: PCA use (morphine or morphine and ketamine, mg/24h)



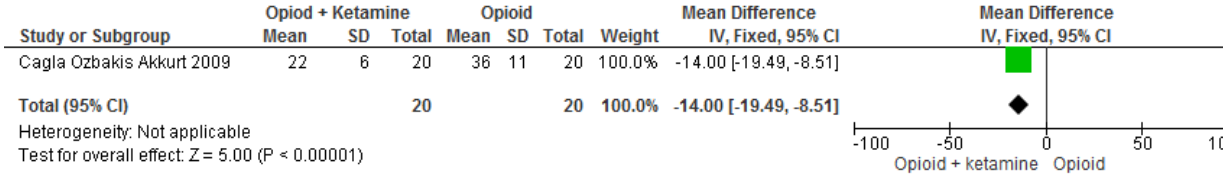
6

Figure 152: Rescue analgesic interventions (0-24 hours)



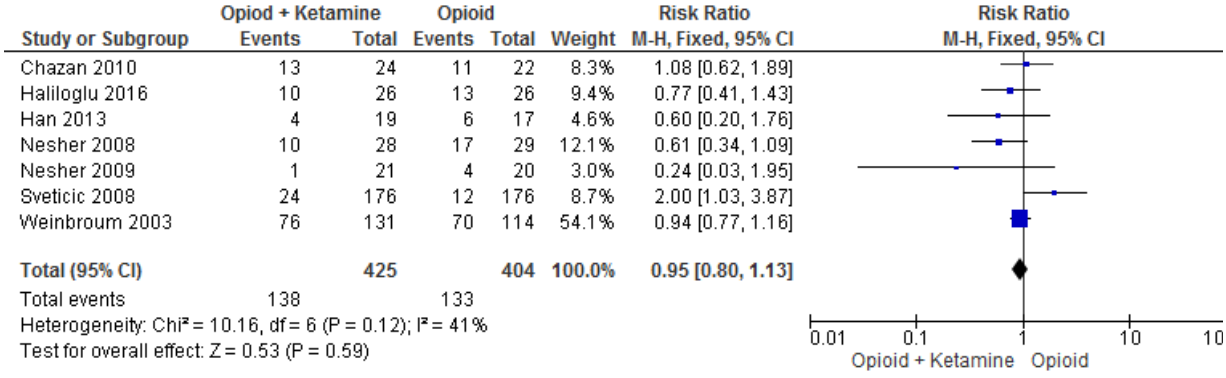
1

Figure 153: Rescue Meperidine consumption



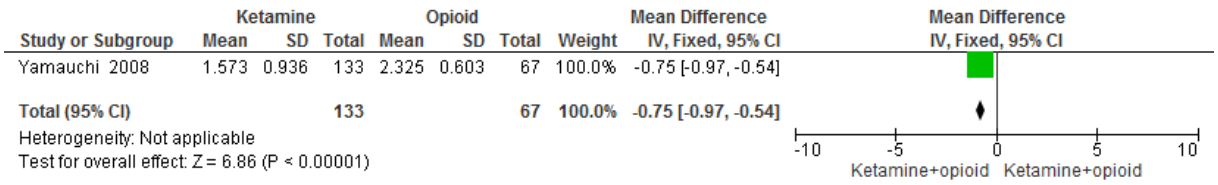
2

Figure 154: Requiring NSAIDs



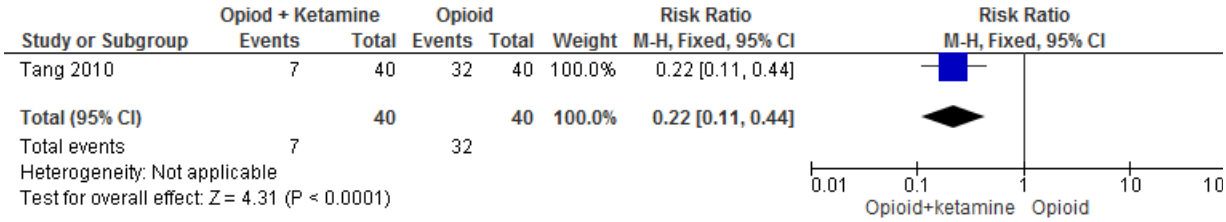
3

Figure 155: Rescue NSAID requirement (mean times)



4

Figure 156: Rescue Propofol (number of people)



5

Figure 157: Rescue Propofol (mean dose)

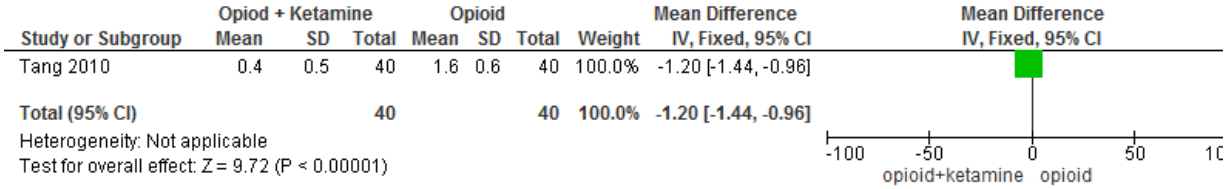


Figure 158: Rescue paracetomol needed

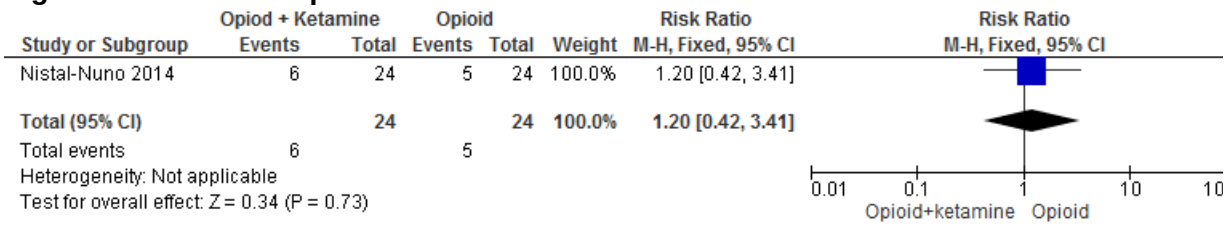


Figure 159: Rescue Tramadol needed

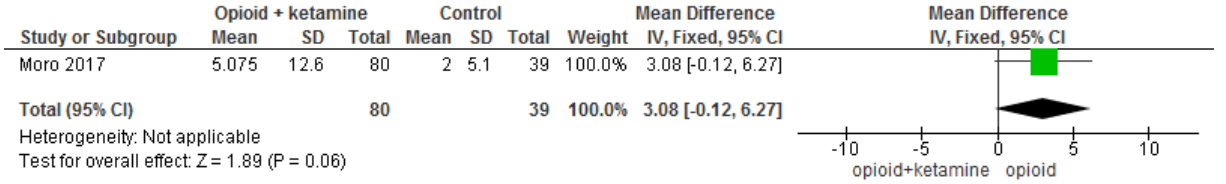


Figure 160: Additional Metamizole

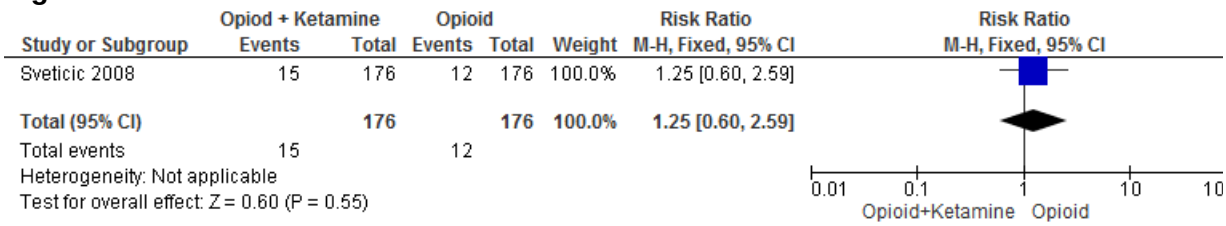


Figure 161: Mean Remifentanil dose (µg/kg-1/min-1)

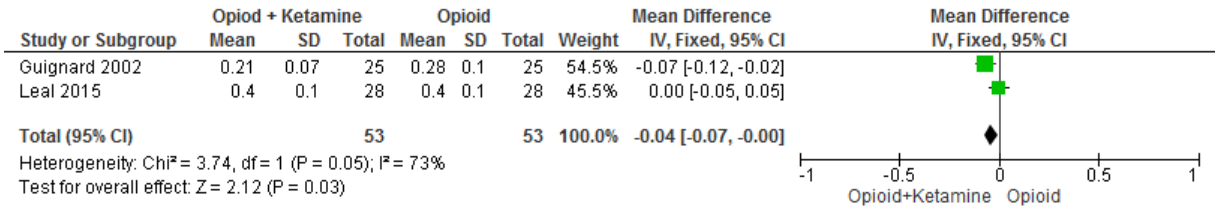


Figure 162: Psychological distress – Delirium rating scale 48 hours

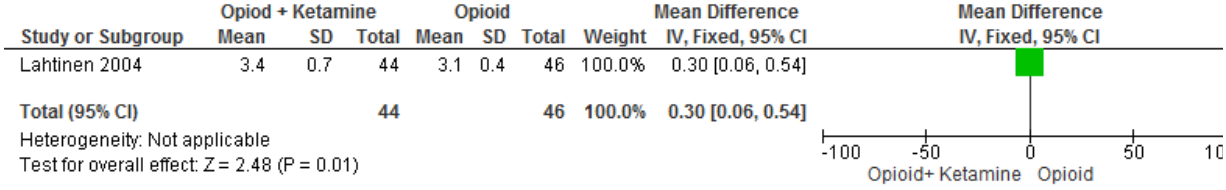
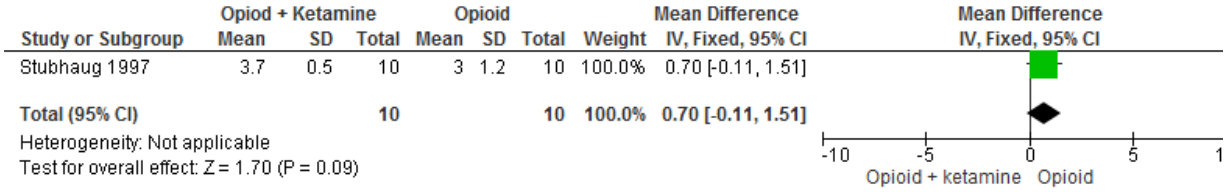
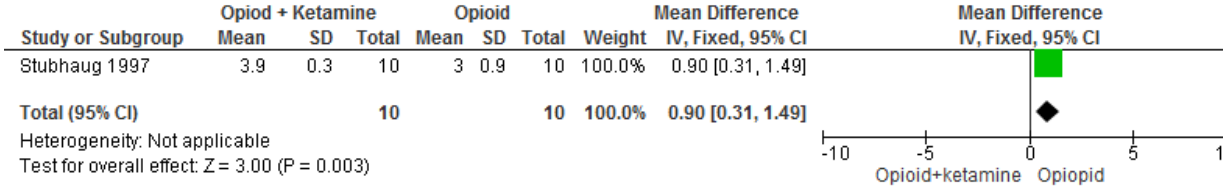


Figure 163: Psychological distress – Global assessment score day 3



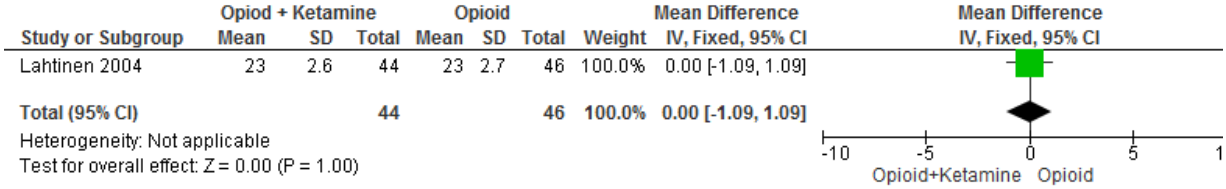
1

Figure 164: Psychological distress - Global assessment score day 7



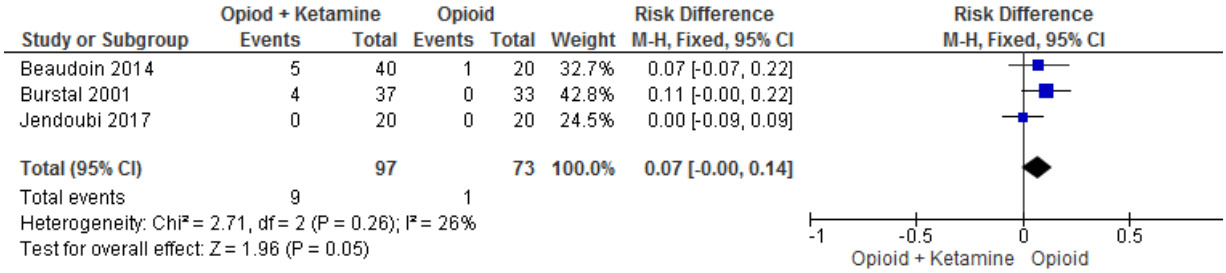
2

Figure 165: Psychological distress – Mini mental state examination – 48 hours



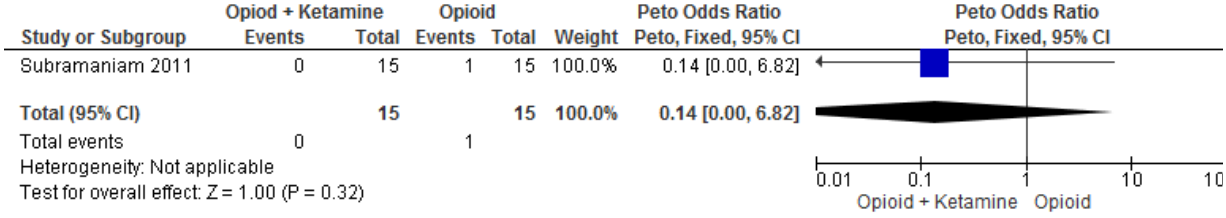
3

Figure 166: Psychological distress – Dysphoria



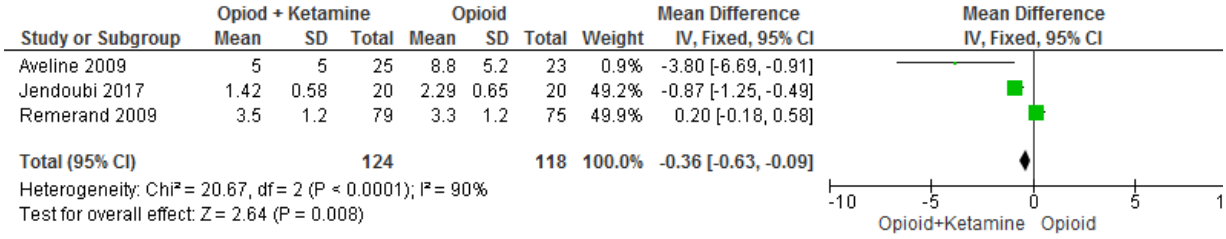
4

Figure 167: Psychological distress – Severe depression



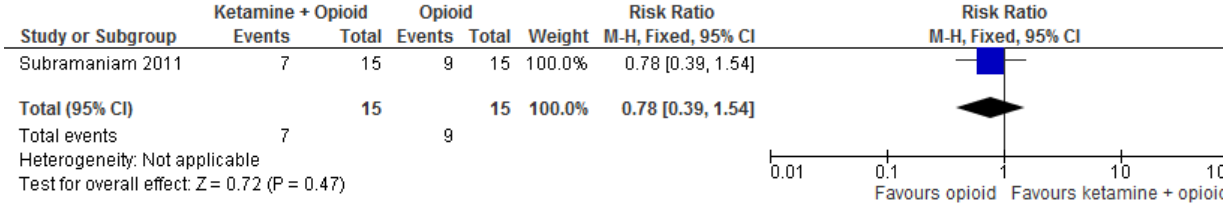
5

Figure 168: Functional measure - time to mobilisation (days)



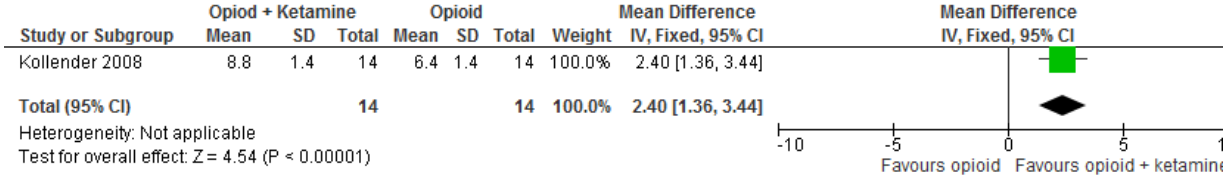
1

Figure 169: Functional measure – mobilised within 48 hours



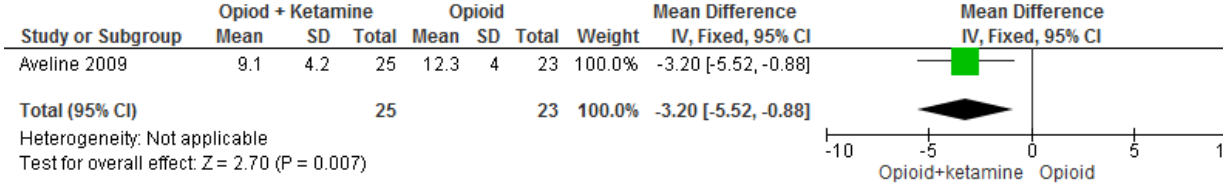
2

Figure 170: Functional measure – Physical performance



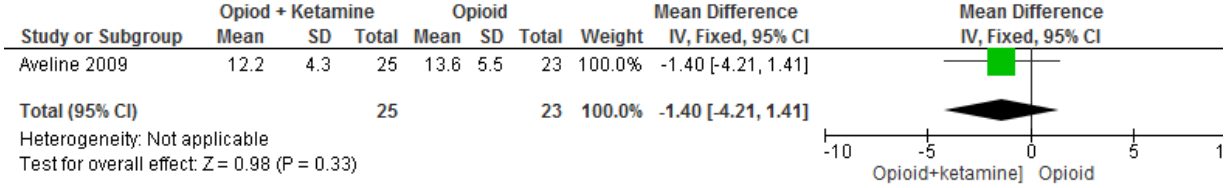
3

Figure 171: Functional measure – time to 90 degree knee flexion (days)



4

Figure 172: Functional measure – time to maximal knee flexion



5

6

Figure 173: Length of Hospital stay

Study or Subgroup	Opiod + Ketamine Mean	SD	Total	Opioid Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aveline 2009	12	2.5	25	14.1	3.8	23	22.5%	-2.10 [-3.94, -0.26]
Jendoubi 2017	5.5	0.7	20	7.7	2.1	20	29.1%	-2.20 [-3.17, -1.23]
Kwok 2004	2.9	0.5	45	3	0.8	45	32.6%	-0.10 [-0.38, 0.18]
Subramaniam 2011	6.73	5.23	15	4.8	1.82	15	15.8%	1.93 [-0.87, 4.73]
Total (95% CI)			**105**			**103**	**100.0%**	**-0.84 [-2.39, 0.70]**

Heterogeneity: Tau² = 1.89; Chi² = 22.85, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 1.07 (P = 0.29)

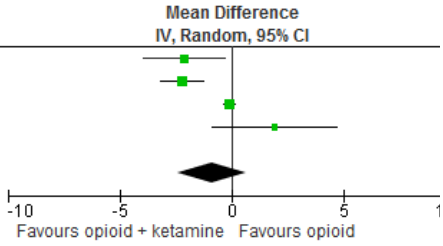


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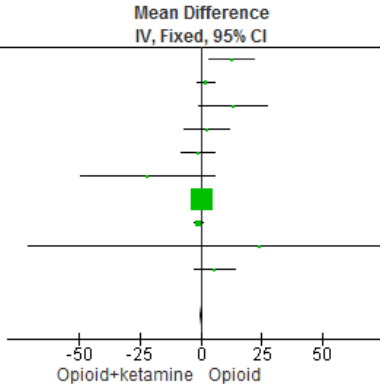
Figure 174: Length of stay in PACU (minutes)

Study or Subgroup	Opiod + Ketamine Mean	SD	Total	Opioid Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Badrinath 2000	79.57	28.11	75	66.8	17.8	25	0.6%	12.77 [3.33, 22.21]
Deng 2009	63.63	10.58	150	61.7	12	50	3.6%	1.93 [-1.80, 5.66]
Dullenkopf 2009	122.2	44.03	77	108.9	29.1	33	0.3%	13.30 [-0.67, 27.27]
Moro 2017	85.31	27.37	80	82.9	23.9	39	0.5%	2.41 [-7.19, 12.01]
Morue 2018	43	17	61	44	22	60	1.0%	-1.00 [-8.01, 6.01]
Ong 2001	121.5	26.8	20	143.6	56.8	20	0.1%	-22.10 [-49.63, 5.43]
Remerand 2009	8.8	3.2	79	8.3	1.6	75	79.5%	0.50 [-0.29, 1.29]
Safavi 2011	30.1	3.4	30	31.2	4.1	30	13.8%	-1.10 [-3.01, 0.81]
Subramaniam 2011	233.4	175.38	15	209.33	70.02	15	0.0%	24.07 [-71.50, 119.64]
Tang 2010	103.1	19.3	40	97.4	18.2	40	0.7%	5.70 [-2.52, 13.92]
Total (95% CI)			**627**			**387**	**100.0%**	**0.45 [-0.25, 1.16]**

Heterogeneity: Chi² = 17.65, df = 9 (P = 0.04); I² = 49%
Test for overall effect: Z = 1.25 (P = 0.21)



2

3

Appendix E: GRADE tables

Table 35: Clinical evidence profile: IV Ketamine and IV Opioid compared to IV opioid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioid + Ketmaine		Relative (95% CI)	Absolute		
Pain: VAS (follow-up <6 hours ; range of scores: 0-10; Better indicated by lower values)												
25	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	795	710	-	MD 1.06 lower (1.72 to 0.41 lower)	⊕⊕OO LOW	CRITICAL
Pain: VAS (follow-up 6-24 hours; range of scores: 0-10; Better indicated by lower values)												
31	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	1269	1086	-	MD 0.68 lower (0.96 to 0.41 lower)	⊕⊕OO LOW	CRITICAL
Pain-none (follow-up 4 hours)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	0/24 (0%)	0%	Risk Difference 0 (-0.15 to 0.15)	0 fewer per 1000 (from 150 fewer to 150 more)	⊕OOO VERY LOW	CRITICAL
Pain- Mild (follow-up 4 hours)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/24 (54.2%)	0%	Peto OR 9.03 (1.93 to 42.26)	Not estimable	⊕⊕⊕O MODERATE	CRITICAL

Pain- Moderate (follow-up 4 hours)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/24 (41.7%)	55.6%	RR 0.75 (0.35 to 1.59)	139 fewer per 1000 (from 361 fewer to 328 more)	⊕OOO VERY LOW	CRITICAL
Pain- Severe (follow-up 4 hours)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/24 (25%)	44.4%	RR 0.56 (0.21 to 1.54)	195 fewer per 1000 (from 351 fewer to 240 more)	⊕OOO VERY LOW	CRITICAL
Pain- Very severe (follow-up 4 hours)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/24 (4.2%)	11.1%	RR 0.38 (0.03 to 5.38)	69 fewer per 1000 (from 108 fewer to 486 more)	⊕OOO VERY LOW	CRITICAL
Pain-none (follow-up 24 hours)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/39 (28.2%)	11.1%	RR 2.06 (0.56 to 7.55)	118 more per 1000 (from 49 fewer to 727 more)	⊕OOO VERY LOW	CRITICAL
Pain-Mild (follow-up 24 hours)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	17/39 (43.6%)	46.7%	RR 0.93 (0.52 to 1.65)	33 fewer per 1000 (from 224 fewer to 304 more)	⊕⊕OO LOW	CRITICAL
Pain-Moderate (follow-up 24 hours)												
2	randomised	no serious	serious[1]	no serious	very serious[3]	none	10/39	42.2%	RR 0.63 (0.16 to	156 fewer per 1000	⊕OOO	CRITICAL

	trials	risk of bias		indirectness			(25.6%)		2.51)	(from 354 fewer to 637 more)	VERY LOW	
Pain-Severe (follow-up 24 hours)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/39 (2.6%)	0%	RD 0.04 (-0.08 to 0.16)	40 more per 1000 (from 80 fewer to 160 more)	⊕⊕OO LOW	CRITICAL
Pain-Very severe (follow-up 24 hours)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/24 (0%)	0%	Risk Difference 0 (-0.15 to 0.15)	0 fewer per 1000 (from 150 fewer to 150 more)	⊕⊕⊕O MODERATE	CRITICAL
Pain: patients with no pain												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/15 (66.7%)	13.3%	RR 5 (1.31 to 19.07)	532 more per 1000 (from 41 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Pain: patients with pain												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/15 (33.3%)	86.7%	RR 0.38 (0.18 to 0.81)	538 fewer per 1000 (from 165 fewer to 711 fewer)	⊕⊕OO LOW	CRITICAL
Adverse events mean nausea score (follow-up 24 hours; Better indicated by lower values)												
4	randomised trials	no serious risk of bias[2]	serious[1]	no serious indirectness	no serious imprecision	none	125	81	-	SMD 0.25 lower (0.83 lower to 0.32 higher)	⊕⊕⊕O MODERATE	CRITICAL

Adverse events mean nausea score (follow-up 48 hours; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	156	89	-	SMD 0.29 lower (0.56 to 0.03 lower)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: Nausea												
29	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	355/1289 (27.5%)	30.5%	RR 0.98 (0.88 to 1.1)	6 fewer per 1000 (from 37 fewer to 31 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events: Vomiting												
24	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	118/973 (12.1%)	11.8%	RR 1.17 (0.92 to 1.49)	20 more per 1000 (from 9 fewer to 58 more)	⊕⊕OO LOW	CRITICAL
Adverse events: Nausea and vomiting												
32	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	222/1026 (21.6%)	30%	RR 0.76 (0.66 to 0.88)	72 fewer per 1000 (from 36 fewer to 102 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: Respiratory depression												
6	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[3]	none	56/362 (15.5%)	10%	RR 1.05 (0.77 to 1.42)	5 more per 1000 (from 23 fewer to 42 more)	⊕OOO VERY LOW	CRITICAL
Additional opioid consumption (follow-up <6 hours post-op; Better indicated by lower values)												
18	randomised	no serious	very serious[1]	no serious	no serious	none	650	498	-	SMD 0.91 lower	⊕⊕OO	CRITICAL

	trials	risk of bias		indirectness	imprecision					(1.35 to 0.47 lower)	LOW	
Additional opioid consumption (follow-up 24 hours post-op; Better indicated by lower values)												
44	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	1597	1254	-	SMD 1.25 lower (1.63 to 0.86 lower)	⊕⊕OO LOW	CRITICAL
Requiring additional opioid (follow-up 24 hours)												
8	randomised trials	serious[2]	very serious[1]	no serious indirectness	no serious imprecision	none	86/266 (32.3%)	57.1%	RR 0.62 (0.38 to 0.99)	217 fewer per 1000 (from 6 fewer to 354 fewer)	⊕OOO VERY LOW	CRITICAL
Morphine injections (per patient); Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	131	114	-	MD 1.17 lower (1.31 to 1.03 lower)	⊕⊕⊕O MODERATE	CRITICAL
PCA Fentanyl infusion rate (follow-up <6 hours; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 0.1 higher (0.24 lower to 0.44 higher)	⊕⊕OO LOW	CRITICAL
PCA Fentanyl infusion rate (follow-up 24 hours; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 0 higher (0.24 lower to 0.24 higher)	⊕⊕⊕O MODERATE	
PCA use (morphine or morphine+ketamine) (follow-up 24 hours; Better indicated by lower values)												
3	randomised trials	serious[2]	serious[1]	no serious indirectness	no serious imprecision	none	149	129	-	MD 15.7 lower (35.84 to 4.44 lower)	⊕⊕OO LOW	

Rescue analgesic interventions (follow-up 24 hours)											
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/254 (22.8%)	45.5%	RR 0.54 (0.4 to 0.72)	209 fewer per 1000 (from 127 fewer to 273 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Rescue Meperidine consumption (Better indicated by lower values)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 14 lower (19.49 to 8.51 lower)	⊕⊕⊕O MODERATE	CRITICAL
Requiring rescue NSAIDs											
7	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	138/425 (32.5%)	50%	RR 0.95 (0.8 to 1.13)	25 fewer per 1000 (from 100 fewer to 65 more)	⊕⊕⊕O MODERATE	CRITICAL
Rescue NSAID requirement (mean times) (follow-up mean 48 hours; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	130	67	-	MD 0.75 lower (0.97 to 0.54 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Requiring rescue propofol											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/40 (17.5%)	80%	RR 0.22 (0.11 to 0.44)	624 fewer per 1000 (from 448 fewer to 712 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Rescue propofol (mean dose) (Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness		none	40	40	-	MD 1.2 lower (1.44 to 0.96 lower)		CRITICAL

Rescue paracetamol needed												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	6/24 (25%)	20.8%	RR 1.2 (0.42 to 3.41)	42 more per 1000 (from 121 fewer to 501 more)	⊕⊕OO LOW	CRITICAL
Rescue Tramadol consumption (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	80	39	-	MD 3.08 higher (0.12 lower to 6.27 higher)	⊕⊕OO LOW	CRITICAL
Additional Metamizole												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	15/176 (8.5%)	6.8%	RR 1.25 (0.6 to 2.59)	17 more per 1000 (from 27 fewer to 108 more)	⊕⊕OO LOW	CRITICAL
Mean remfentanil dose (µg/kg-1/min-1) (follow-up 24 hours; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	53	-	MD 0.04 lower (0.07 lower to 0 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Psychological distress - Delirium rating scale (follow-up 2 days; range of scores: 0-32; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	44	46	-	MD 0.3 higher (0.06 to 0.54 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Psychological distress Global assessment score (follow-up 3 days; range of scores: 0-4; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	10	10	-	MD 0.7 higher (0.11 lower to 1.51 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Psychological distress Global assessment score (follow-up 7 days; range of scores: 0-4; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	10	10	-	MD 0.9 higher (0.31 to 1.49 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Psychological distress - mini mental state examination (follow-up 2 days; range of scores: 0-30; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	44	46	-	MD 0 higher (1.09 lower to 1.09 higher)	⊕⊕⊕O MODERATE	
Psychological distress - Dysphoria												
3	randomised trials	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9/97 (9.3%)	1.4%	Risk Difference 0.07 (0 to 0.14)	70 more per 1000 (from 0 fewer to 140 more)	⊕⊕⊕O MODERATE	IMPORTANT
Psychological distress - Severe depression												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/15 (0%)	6.7%	Peto OR 0.14 (0 to 6.82)	58 fewer per 1000 (from 67 fewer to 390 more)	⊕⊕OO LOW	IMPORTANT
Functional measusre (time to walk, days) (Better indicated by lower values)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	124	118	-	MD 0.36 lower (0.63 to 0.09 lower)	⊕⊕OO LOW	CRITICAL
Functional measusre: Mobilisation within 48hr												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	7/15 (46.7%)	60%	RR 0.78 (0.39 to 1.54)	132 fewer per 1000 (from 366 fewer to	⊕⊕OO LOW	IMPORTANT

										324 more)		
Functional measure: physical performance (follow-up 4 days; range of scores: 0-10; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	14	-	MD 2.4 higher (1.36 to 3.44 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Functional measure (Time to 90 degree knee flexion) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	25	23	-	MD 3.2 lower (5.52 to 0.88 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Functional measusre (time to maximal knee flexion) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	25	23	-	MD 1.4 lower (4.21 lower to 1.41 higher)	⊕⊕⊕O MODERATE	
Length of hospital stay (Better indicated by lower values)												
4	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	105	103	-	MD 0.84 lower (2.39 lower to 0.70 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Length of stay in PACU (Better indicated by lower values)												
10	randomised trials	no serious risk of bias[2]	serious[1]	no serious indirectness	no serious imprecision	none	627	387	-	MD 0.45 higher (0.25 lower to 1.16 higher)	⊕⊕⊕O MODERATE	

[1] Downgraded by 1 or 2 increments due to heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix F:Excluded studies

F.1 Excluded clinical studies

Table 36: Studies excluded from the clinical review

Study	Exclusion reason
Abdel-Ghaffar 2014[4]	Inappropriate intervention/comparison
Abdolahi 2013[6]	Inappropriate intervention
Abrishamkar 2012[7]	Inappropriate comparison
Adriaenssens 1999[11]	Unclear dosage
Agarwal 2001[14]	Inappropriate comparison
Aida 2000[18]	Inappropriate intervention/comparison
Andonov 1998[40]	Inappropriate study design
Aqil 2011[43]	Inappropriate intervention
Argiriadou 2004[45]	Inappropriate intervention/comparison
Argiriadou 2011[46]	Inappropriate intervention
Assouline 2016[52]	Systematic review: references checked
Atanasova 2015[54]	Not in English
Atangana 2007[55]	Inappropriate study design
Barreveld 2013[78]	Inappropriate population
Batra 2005[83]	Inappropriate intervention/comparison
Behdad 2013[91]	Inappropriate intervention/comparison
Beilin 2007[92]	Inappropriate intervention/comparison
Bell 2005[94]	Systematic review: references checked
Bell 2006[95]	Systematic review: references checked
Bennett 2016[97]	Inappropriate study design
Bhattacharya 1994[105]	Inappropriate intervention/comparison
Borner 2007[120]	Not in English
Brinck 2018[130]	Systematic review: references checked
Bristow 1989[131]	Inappropriate intervention
Canbay 2008[144]	Inappropriate population
Carstensen 2010[149]	Systematic review: references checked
Cha 2012[153]	Inappropriate population
Chapman 2019[159]	Systematic review: references checked
Chen 2004[163]	Inappropriate intervention
Chia 1998[171]	Inappropriate comparison
Choi 2016[177]	Inappropriate intervention/comparison
Cogan 2017[193]	Inappropriate study design
Colombani 2008[197]	Not in English
Crousier 2008[208]	Not in English
Dal 2005[215]	Inappropriate intervention
Dilli 2008[244]	Inappropriate population
Duncan 2016[256]	Inappropriate intervention
Elia 2005[267]	Systematic review: references checked
Elkassem 2008[269]	Inappropriate intervention/comparison

Study	Exclusion reason
Forget 2017[301]	Systematic review: references checked
Furuya 2001[310]	Inappropriate intervention/comparison
Galinski 2007[312]	Inappropriate comparison
Galinski 2007[311]	Inappropriate population
Garcia-Henares 2018[319]	Systematic review: references checked
Gonul 2015[338]	Inappropriate comparison
Goyal 2016[341]	Inappropriate comparison
Grace 2001[342]	Inappropriate comparison
Grady 2012[343]	Inappropriate intervention/comparison
Gurnani 1996[362]	Inappropriate intervention/comparison
Hadhimane 2016[364]	Inappropriate intervention
Heesen 2015[389]	Systematic review: references checked
Heidari 2013[393]	Not in English
Heidari-Tabaee-Zavare 2015[392]	Not in English
Hercock 1999[394]	Inappropriate study design
Himmelseher 2001[398]	Inappropriate intervention
Hong 1999[404]	Not in English
Hu 2014[412]	Inappropriate no relevant outcomes/incorrect population
Iwata 2010[433]	Inappropriate intervention
Jennings 2011[445]	Systematic review: references checked
Jennings 2014[446]	Inappropriate population
Jensen 2008[447]	Inappropriate population
Jonkman 1000[459]	Systematic review: references checked
Joseph 2012[463]	Inappropriate intervention/comparison
Jouguelet-Lacoste 2015[467]	Systematic review: references checked
Jung 2005[468]	Not in English
Kafali 2004[470]	Inappropriate study design
Kakinohana 2004[477]	Inappropriate intervention
Kamal 2008[479]	Inappropriate population
Karaman 2006[487]	Not in English
Kararmaz 2003[488]	Inappropriate intervention/comparison
Karcioglu 2013[491]	Inappropriate intervention
Kashefi 2006[493]	Inappropriate Conference abstract
Kawana 1987[497]	Inappropriate intervention/comparison
Khashan 2016[507]	Inappropriate intervention/comparison
Kim 2001[511]	Not in English
Kim 2006[516]	Not in English
Klatt 2015[534]	Systematic review: references checked
Kose EA 2013[546]	Inappropriate intervention/comparison
Kudoh 2002[556]	Inappropriate intervention
Kwon 2009[563]	Not in English
Laskowski 2011[572]	Systematic review: references checked
Lauretti 1996[575]	Inappropriate intervention
Lebrun 2006[580]	Inappropriate intervention
Lee 2001[588]	Not in English

Study	Exclusion reason
Lee 2005[587]	Not in English
Lee 2008[586]	Not in English
Lehmann 2001[595]	Not in English
Levanen 2000[602]	Inappropriate comparison
Lin 2016[618]	Inappropriate intervention/comparison
Liu 2012[630]	Systematic review: references checked
Loftus 2010[634]	Inappropriate population
Lohit 2011[636]	Inappropriate study design
Lou 2017[639]	Not in English
Martinez 2016[673]	Inappropriate study design
Mathews 2012[677]	Systematic review: references checked
Mathisen 1995[681]	Inappropriate study design
Maurset 1989[686]	Inappropriate study design
McCartney 2004[688]	Systematic review: references checked
McNicol 2014[694]	Systematic review: references checked
Mendola 2012[702]	Inappropriate intervention/comparison
Menkiti 2012[708]	Inappropriate comparison
Nesek-Adam 2012[903]	Inappropriate intervention
Messenger 2008[712]	Inappropriate intervention/comparison
Miller 2015[721]	Inappropriate population
Mortero 2001[758]	Inappropriate intervention/comparison
Motov 2015[766]	Inappropriate intervention
Motov 2016[767]	Systematic review: references checked
Moyse 2017[770]	Systematic review: references checked
Nalini 2014[785]	Inappropriate intervention/comparison
NCT 2005[792]	Citation only
NCT 2006[793]	Citation only
NCT 2008[809]	Citation only
NCT 2008[812]	Citation only
NCT 2009[826]	Citation only
NCT 2010[831]	Citation only
NCT 2010[836]	Citation only
NCT 2010[834]	Citation only
NCT 2011[839]	Citation only
NCT 2012[845]	Citation only
NCT 2015[869]	Citation only
NCT 2015[868]	Citation only
NCT 2015[865]	Citation only
NCT 2015[863]	Citation only
NCT 2015[862]	Citation only
NCT 2016[878]	Citation only
NCT 2016[874]	Citation only
NCT 2017[895]	Citation only
NCT 2017[892]	Citation only
NCT 2017[896]	Citation only

Study	Exclusion reason
NCT 2017[887]	Citation only
NCT 2017[893]	Citation only
NCT 2018[898]	Citation only
NCT 2018[899]	Citation only
NCT 2018[900]	Citation only
Neuhauser 2008[909]	Inappropriate intervention/comparison
Öğün 2001[932]	Not in English
Ozgun 2003[952]	Not in English
Papaziogas 2001[970]	Inappropriate intervention
Park 1998[978]	Not in English
Parkhouse 1977[985]	Inappropriate intervention
Pendi 2018[992]	Systematic review: references checked
Radvansky 2015[1027]	Systematic review: references checked
Rahimi 2012[1031]	Not in English
Sami Mebazaa 2008[1096]	Not in English
Schmid 1999[1111]	Systematic review: references checked
Sen 2005[1124]	Inappropriate comparison
Shah 2006[1134]	Inappropriate comparison
Silva 2012[1146]	Inappropriate comparison
Snijdelaar 2004[1176]	Inappropriate comparison
Souzdalnitski 2014[1182]	Systematic review: references checked
Spreng 2010[1185]	Inappropriate intervention/comparison
Stuardo 2017[1204]	Systematic review: references checked
Subramaniam 2001[1206]	Inappropriate intervention/comparison
Subramaniam 2001[1208]	Inappropriate intervention/comparison
Subramaniam 2004[1209]	Systematic review: references checked
Suppa 2012[1218]	Inappropriate comparison
Suzuki 2006[1220]	Inappropriate intervention/comparison
Tan 1999[1235]	Inappropriate intervention
Tan 2019[1236]	Inappropriate comparison
Taura 2003[1246]	Inappropriate comparison
Tena 2014[1250]	Inappropriate intervention
Terracina 2018[1253]	Systematic review: references checked
Treskatsch 2014[1265]	Inappropriate comparison
Tuman 1988[1269]	Inappropriate comparison
Tuncali 2015[1272]	Inappropriate intervention
Urban 2008[1291]	Inappropriate study design
Van Elstraete 2004[1303]	Inappropriate intervention
Viscomi 2009[1316]	Inappropriate comparison
Wang 2006[1334]	Inappropriate intervention/comparison
Wang 2016[1331]	Systematic review: references checked
Wanna 2004[1335]	Inappropriate comparison/ no relevant outcomes
Webb 2007[1343]	Inappropriate intervention
Wong 1997[1361]	Inappropriate comparison
Woo 2014[1364]	Inappropriate intervention

Study	Exclusion reason
Wu 2000[1367]	Inappropriate intervention
Xie 2003[1371]	Inappropriate comparison
Yang 1999[1387]	Not in English
Yang 2014[1389]	Systematic review: references checked
Yazigi 2012[1397]	Inappropriate intervention/comparison
Ye 2017[1398]	Systematic review: references checked
Yentur 2004[1400]	Not in English
Ysasi 2010[1414]	Not in English
Yun 2000[1418]	Not in English
Yung 1997[1419]	Inappropriate intervention/comparison
Zgaia 2015[1430]	Systematic review: references checked
Zhu 2018[1441]	Systematic review: references checked

F.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 37: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Neuropathic nerve stabilisers

Appendix A: Review protocols

Table 38: Review protocol: Managing acute postoperative pain: Neuropathic nerve stabilisers

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	What is the most clinically and cost effective strategy for managing acute postoperative pain?
2.	Review question	What is the most clinically and cost effective strategy for managing acute postoperative pain? There are six topic areas that have been identified: Paracetamol routes of delivery Non-steroidal anti-inflammatory drugs (NSAIDs) Opioid administration strategy (Continuous epidural ,intravenous PCA, spinal) Opioid post-operative administration strategy (oral vs iv) Ketamine Neuropathic nerve stabilisers This protocol addresses, 'What is the clinical and cost effectiveness of neuropathic nerve stabilisers in managing acute post-operative pain?'
3.	Objective	To determine if neuropathic nerve stabilisers are clinically and cost effective in managing acute post-operative pain.
4.	Searches	The following databases will be searched: • Embase • MEDLINE • The Cochrane Library Searches will be restricted by: • English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.

		The full search strategies will be published in the final review.
5.	Condition or domain being studied	What is the most clinically and cost effective strategy for managing acute postoperative pain
6.	Population	Inclusion: Adults (18 years and older) who have undergone surgery. Exclusion: People who have had Surgery for burns, traumatic brain injury or neurosurgery
7.	Intervention/Exposure/Test	Interventions: neuropathic nerve stabilisers with opioids Including • pregabalin • gabapentin • nortriptyline • amitriptyline
8.	Comparator/Reference standard/Confounding factors	Comparators: • opioids • each other
9.	Types of study to be included	Randomised controlled trials and systematic reviews of randomised controlled trials
10.	Other exclusion criteria	Non-English language Cross-over randomised controlled trials
11.	Context	NA
12.	Primary outcomes (critical outcomes)	• Health-related quality of life • Pain reduction o < 6 hours post op o 6 hours- 24 hours post op Pain reduction measured by: • patient reported pain (physician, nurse or carer reported pain will not be included); • patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both) • patient reported pain intensity expressed hourly over four to six hours using validated pain scales, or reported summed pain intensity difference (SPID) at four to six hours • Number of participants achieving at least 50% pain relief • Time to achieve 50% pain intensity • Amount of additional medication use (rescue medication) o < 6 hours post op o 6 hours- 24 hours post op

		• Time to rescue medication • Adverse events (including respiratory depression, nausea, vomiting)
13.	Secondary outcomes (important outcomes)	• Psychological distress and mental well-being • Symptom scores • Functional measures • Length of stay in intensive care • Length of stay in hospital • Hospital readmission The committee agreed that a difference of 1 (10%) on a 10 point pain scale such as NRS or VRS indicated a clinically important difference. For the remaining outcomes, the committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Cochrane RoB (2.0) will be used to assess intervention reviews 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5).

		GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management The clinical approach to this area of the scope is multimodal. The pain management approach for each patient will depend on many factors and include the procedure and the severity of pain. For this reason it is not meaningful to compare the drugs listed in the topic areas to each other. There isn't an overall question evaluating which drug is the most effective and a network meta-analysis is not appropriate.		
17.	Analysis of sub-groups	Subgroups: • people aged over 60 years • surgery grade based on NICE preoperative tests for elective surgery guideline categorisation • American Society of Anesthesiologists (ASA) Physical Status grade • Opioid tolerant populations		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	NA		
22.	Anticipated completion date	NA		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias	☐	☑

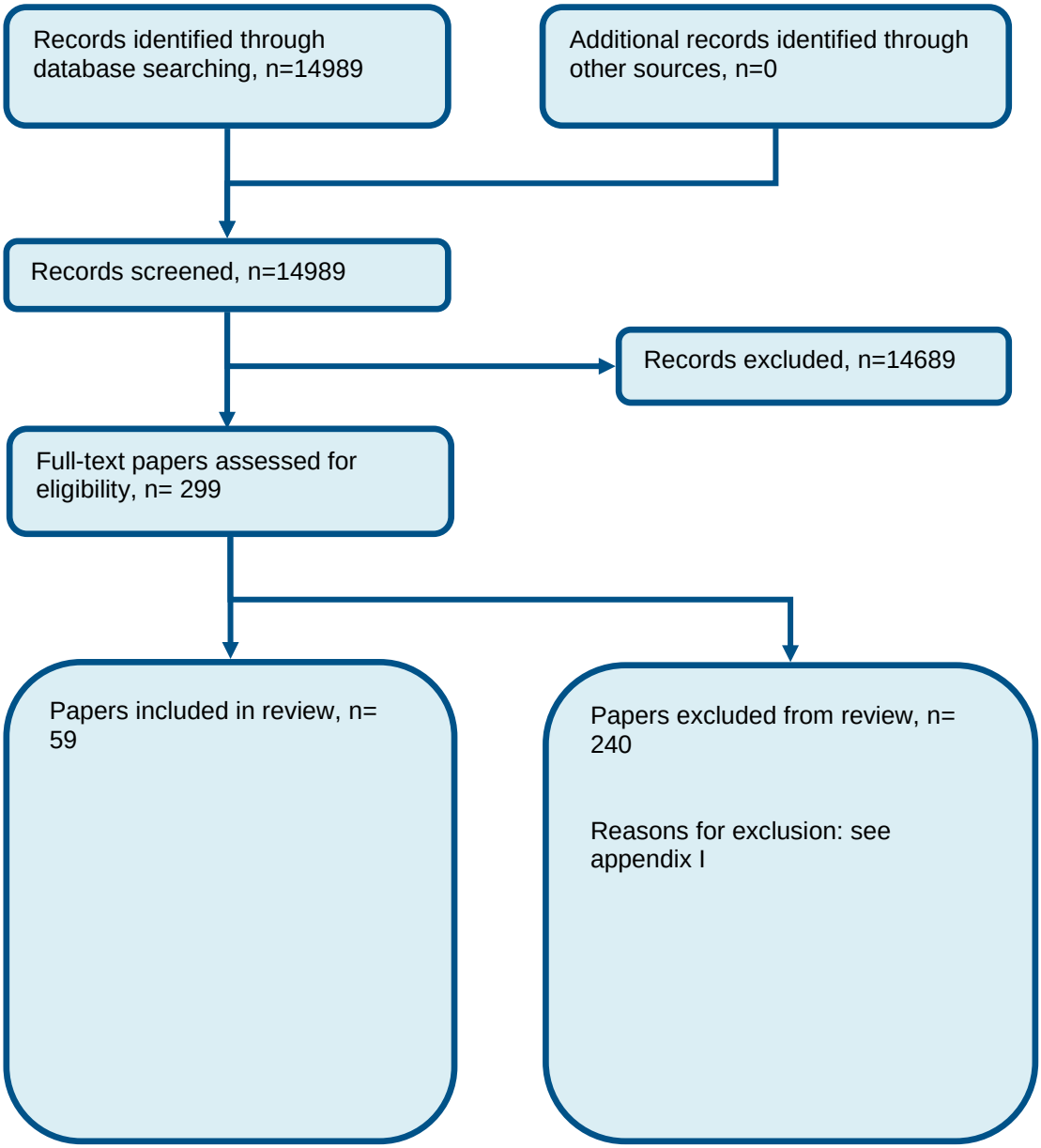
		(quality) assessment		
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swaine Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis Ms Lina Gulhane		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details	NA	
30.	Reference/URL for published protocol	NA	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • Issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Perioperative care Pain relief Paracetamol	
33.	Details of existing review of same topic by same authors	NA	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	NA	
36.	Details of final publication	www.nice.org.uk	

The health economic review protocol is shown in Table **3**.

Appendix B: Clinical evidence selection

Figure 175: Flow chart of clinical study selection for the review of neuropathic nerve stabilisers



Appendix C: Clinical evidence tables

Study	Abdelmageed 2010[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Saudi Arabia; Setting: King Abdulaziz Naval base Hospital, Saudi Arabia
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 - 35 old, ASA I - II scheduled for tonsillectomy under general anesthesia
Exclusion criteria	body weight exceeding 20% of ideal body weight, known allergy to gabapentin, chronic pain, daily intake of analgesics or corticosteroids, and impaired liver or kidney functions.
Recruitment/selection of patients	patients scheduled for tonsillectomy under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 31.4 ± 7.7; Placebo 29.8 ± 6.5. Gender (M:F): Unclear. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 31.4 ± 7.7; Placebo 29.8 ± 6.5). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: Not applicable (Tonsillectomy).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 1200mg oral gabapentin 2 hours before surgery. Duration preoperatively. Concurrent medication/care: Meperidine 1mg/kg IM every 6 hours was given for postoperative pain relief if pain score ≥ 3 or if requested by the patient (n=30) Intervention 2: Opioid only. placebo given 2 hours before surgery. Duration preoperatively. Concurrent medication/care: Meperidine 1mg/kg IM every 6 hours was given for postoperative pain relief if pain score ≥ 3 or if requested by the patient. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO	

Study	Abdelmageed 2010[5]
	Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: pain score 6 hours at 6 hours postoperatively; Group 1: mean 3.2 pain score (SD 0.8); n=30, Group 2: mean 2.1 pain score (SD 0.6); n=30; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value < 0.001 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: pain score 24 hours at 24 hours postoperatively; Group 1: mean 2.1 pain score (SD 0.4); n=30, Group 2: mean 1 pain score (SD 0.7); n=30; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value < 0.001 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Total meperidine consumption at 24 hours postoperatively; Group 1: mean 48.8 milligrams (SD 9.7); n=30, Group 2: mean 93.8 milligrams (SD 8.4); n=30; Comments: p value < 0.001 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Nausea at ~24 hours postoperatively; Group 1: 5/30, Group 2: 13/30; Comments: p value 0.642 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at ~24 hours postoperatively; Group 1: 2/30, Group 2: 9/30; Comments: p value 0.045 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Dizziness at ~24 hours postoperatively; Group 1: 6/30, Group 2: 5/30; Comments: p value 1.0 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Somnolance at ~24 hours postoperatively; Group 1: 2/30, Group 2: 1/30; Comments: p value 1.0 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Sedation at ~24 hours postoperatively; Group 1: 6/30, Group 2: 5/30; Comments: p value 0.497 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom

Study	Abdelmageed 2010[5]
	scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Agarwal 2008[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in India; Setting: Department of Anaesthesiology, Institute of Medical Sciences, Lucknow, India
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I and II, undergoing laparoscopic cholecystectomy under general anaesthesia.
Exclusion criteria	Patients with impaired kidney or liver functions, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, uncontrolled medical disease (diabetes mellitus and hypertension), history of intake of non-steroidal anti-inflammatory drugs within 24 h before surgery, and inability to operate patient-controlled analgesia (PCA) device were excluded from the study.
Recruitment/selection of patients	Scheduled for laparoscopic cholecystectomy
Age, gender and ethnicity	Age - Mean (range): Pregabalin: 46.6 (25–76); Placebo: 44.6 (22–69). Gender (M:F): 41/19. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 46.6 (25–76); Placebo: 44.6 (22–69)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (laparoscopic cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. pregabalin 150 mg 1h before the induction of anesthesia with sips of water by a staff nurse who was not involved in the study. Duration preoperatively. Concurrent medication/care: In the PACU, patients received i.v. fentanyl via PCA with patient activated dose of 20 mg, lockout interval of 5 min, with a maximum allowable fentanyl dose being 2 mg/kg/h. Indirectness: No indirectness (n=30) Intervention 2: Opioid only. Placebo 1h before the induction of anesthesia with sips of water by a staff

Study	Agarwal 2008[13]
	nurse who was not involved in the study. Duration preoperatively. Concurrent medication/care: In the PACU, patients received i.v. fentanyl via PCA with patient activated dose of 20 mg, lockout interval of 5 min, with a maximum allowable fentanyl dose being 2 mg/kg/h. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score 0-4 hours at 0-4 hours postoperative; Median (IQR): Pregabalin: 3.0 (2.0); Placebo: 4.0 (3.8) visual analogue scale 0-10 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Dropouts; Group 2 Number missing: 1, Reason: dropouts

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 12-24 hours at 12-24 hours postoperative; Median (IQR): Pregablin: 2.0 (2.0); Placebo: 3.5 (4.0) visual analogue scale 0-10 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Dropouts; Group 2 Number missing: 1, Reason: dropouts

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: total postoperative fentanyl consumption at postoperative; Median (IQR): Pregabalin: 555.2 (124.8); Placebo: 757.5 (99.3) Micrograms);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Dropouts; Group 2 Number missing: 1, Reason: dropouts

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Sedation at postoperative; Median (IQR): Pregabalin: 3 (1); Placebo: 2 (1) Sedation Score 1-6 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Dropouts; Group 2 Number missing: 1, Reason: dropouts
- Actual outcome: Nausea & Vomiting at postoperative; Group 1: 14/27, Group 2: 15/29
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Agarwal 2008[13]
- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Dropouts; Group 2 Number missing: 1, Reason: dropouts - Actual outcome: Headache at postoperative; Group 1: 8/27, Group 2: 6/29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Dropouts; Group 2 Number missing: 1, Reason: dropouts - Actual outcome: Respiratory Depression at postoperative; Group 1: 1/27, Group 2: 0/29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Dropouts; Group 2 Number missing: 1, Reason: dropouts	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Ajori 2012[19]
Study type	Systematic Review
Number of studies (number of participants)	(n=170)
Countries and setting	Conducted in Iran; Setting: Tajrish Hospital in Tehran, Iran.
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria were ASA class I and II, nonmalignant status (benign gynecologic disease), general anesthesia, and body mass index (BMI) of 20–30 kg/m2 .
Exclusion criteria	The exclusion criteria were known allergy against gabapentin, epilepsy, motion sickness, previous treatment with gabapentin, chronic pain syndrome, psychiatric disorder and substance abuse, patients who had received analgesics within 48 h before surgery, duration of surgery excess 3 h, and trauma of urinary system or bowel within surgery.
Recruitment/selection of patients	candidates for abdominal hysterectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 49.2 ± 7.1; Placebo: 48.3 ± 8.9. Gender (M:F): all female. Ethnicity: NA

Study	Ajori 2012[19]
Further population details	1. Age: <60 years (Gabapentin: 49.2 ± 7.1; Placebo: 48.3 ± 8.9). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: gynae-oncology (abdominal hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. two 300 mg capsules of gabapentin. The medication was given to the patients about 1 h before induction of anesthesia.. Duration preoperatively. Concurrent medication/care: When VAS scores were 4–7: 0.5 mg/kg of meperidine was given intramuscularly (IM); above 7:1 mg/kg of meperidine was given IM; and when VAS scores were 0 to 3: if patient wanted analgesia: 0.5 mg/kg meperidine was given in the same way.. Indirectness: No indirectness (n=70) Intervention 2: Opioid only. Patients were given two placebo capsules. The medication was given to the patients about 1 h before induction of anesthesia.. Duration preoperatively. Concurrent medication/care: When VAS scores were 4–7: 0.5 mg/kg of meperidine was given intramuscularly (IM); above 7:1 mg/kg of meperidine was given IM; and when VAS scores were 0 to 3: if patient wanted analgesia: 0.5 mg/kg meperidine was given in the same way.. Indirectness: No indirectness
Funding	Funding not stated
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Alimian 2012[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in Iran; Setting: Rasoul-Akram Hospital, Iran
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Study	Alimian 2012[32]
Subgroup analysis within study	Not applicable
Inclusion criteria	18 to 60 years old, being a volunteer to undergo DCR surgery, an ASA status of I or II and presenting a written consent to take part in the study.
Exclusion criteria	Patients with any of the following issues were excluded from the study: history of hypersensitivity to pregabalin or its derivatives, hereditary problems of galactose and glucose, lactation a medical history showing a systematic disease such as a hypertension, diabetes, collagen vascular diseases, ischemic heart diseases, kidney or liver diseases, addiction to opioids and long-term use of aspirin and other NSAIDs.
Recruitment/selection of patients	candidates for DCR surgery hospitalized in the eye ward of Rasoul-Akram Hospital from 2010 to 2011 were elected through simple non-random availability sampling according to inclusion and exclusion criteria in the order of their hospitalization in the wards.
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 41.1 ± 14.1; Placebo: 45.4 ± 15.7. Gender (M:F): 50/30. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 41.1 ± 14.1; Placebo: 45.4 ± 15.7). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (not specified). 3. Type of surgery: Not applicable (Dacryocysto-rhinostomy Surgery).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. Patients in the pregabalin group received 300 mg of oral pregabalin an hour before entering the operation room in the morning of the surgery day. In the last 30 minutes of the op- eration injecting of opioids was prohibited.. Duration one administration. Concurrent medication/care: For the patients whose pain intensity exceeded three on VAS measurement, 25 mg pethedine was administered intramuscularly and documented.. Indirectness: No indirectness (n=40) Intervention 2: Opioid only. the patients in the placebo group received placebo an hour before entering the operation room in the morning of the surgery day. In the last 30 minutes of the operation injecting of opioids was prohibited.. Duration one administration. Concurrent medication/care: For the patients whose pain intensity exceeded three on VAS measurement, 25 mg pethedine was administered intramuscularly and documented.. Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO	

Study	Alimian 2012[32]
Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Nausea at postoperatively; Group 1: 5/40, Group 2: 17/40; Comments: p value 0.003 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 1/40, Group 2: 5/40; Comments: p value 0.09 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Pain score < 6 hours at < 6 hours postoperatively; Group 1: mean 2.5 pain score (SD 1.5); n=40, Group 2: mean 5.1 pain score (SD 1.7); n=40; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value < 0.001 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pain score at 24 hours at 24 hours postoperatively; Group 1: mean 0.6 pain score (SD 0.8); n=40, Group 2: mean 1.6 pain score (SD 1.5); n=40; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value <0.001 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Al-Mujadi 2006[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=78)
Countries and setting	Conducted in India, United Arab Emirates; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Al-Mujadi 2006[22]
Inclusion criteria	ASA I or II scheduled for elective thyroid surgery under general anesthesia
Exclusion criteria	known allergy to gabapentin; a history of drug or alcohol abuse; chronic pain or daily intake of analgesics or corticosteroids; diabetes; or impaired kidney function
Recruitment/selection of patients	scheduled for elective thyroid surgery under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 45±13; Placebo: 49±15. Gender (M:F): 19/53. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 45±13; Placebo: 49±15). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (all patients ASA I or II). 3. Type of surgery: Not applicable (thyroidectomy).
Indirectness of population	--
Interventions	(n=41) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 1200mg of gabapentin two hours before surgery. Duration preoperatively. Concurrent medication/care: Morphine 3mg IV bolus doses were given every 5 minutes until VAS pain scores were 4 or less at rest and 6 or less with swallowing. Metoclopramide 10mg IV was given for nausea and vomiting. . Indirectness: No indirectness (n=37) Intervention 2: Opioid only. placebo capsules two hours before surgery. Duration preoperatively. Concurrent medication/care: Morphine 3mg IV bolus doses were given every 5 minutes until VAS pain scores were 4 or less at rest and 6 or less with swallowing. Metoclopramide 10mg IV was given for nausea and vomiting. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain scores 6 hours postoperatively at 6 hours postoperatively; Group 1: mean 1.4 pain score (SD 0.7); n=37, Group 2: mean 2.41 pain score (SD 1.3); n=35; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: postponement of surgery; broke protocol; Group 2 Number missing: 2, Reason: postponement of surgery; broke protocol

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: pain scores 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 1.8 pain csore (SD 1.6); n=37, Group 2: mean 2.3 pain csore (SD 1.3); n=35; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Al-Mujadi 2006[22]
- Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: postponement of surgery; broke protocol; Group 2 Number missing: 2, Reason: postponement of surgery; broke protocol Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: morphine consumption within 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 15.2 milligrams (SD 7.6); n=37, Group 2: mean 29.5 milligrams (SD 9.9); n=35; Comments: p value 0.001 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: postponement of surgery; broke protocol; Group 2 Number missing: 2, Reason: postponement of surgery; broke protocol Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Urinary Retention at postoperatively; Group 1: 1/37, Group 2: 0/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: postponement of surgery; broke protocol; Group 2 Number missing: 2, Reason: postponement of surgery; broke protocol	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Balaban 2012[69]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Turkey; Setting: Department of Anesthesiology and Reanimation, Türkiye Yüksek Ihtisas Education and Research Hospital, Turkey
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Balaban 2012[69]
Inclusion criteria	>18 years of age and scheduled for laparoscopic cholecystectomy
Exclusion criteria	inability to cooperate, pregnancy, emergency surgical intervention, ASA physical status of 3 or higher, severe renal and/or hepatic dysfunction, history of allergy to pregabalin, limited or insufficient respiratory reserve, conversion to open cholecystectomy, and duration of surgery in excess of 60 minutes.
Recruitment/selection of patients	scheduled for laparoscopic cholecystectomy
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 53.6 ± 13.36; Placebo 51.4 ± 15.7. Gender (M:F): 21/69. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 53.6 ± 13.36; Placebo 51.4 ± 15.7). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (laparoscopic cholecystectomy).
Indirectness of population	--
Interventions	(n=60) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. received pregabalin (150 mg or 300 mg) orally one hour before surgery. None of the patients received other premedication.. Duration preoperative . Concurrent medication/care: If a VAS score was 5 or more, intravenous fentanyl 25 µg was given and repeated if required.. Indirectness: No indirectness (n=30) Intervention 2: Opioid only. oral placebo one hour before surgery. Duration preoperative. Concurrent medication/care: If a VAS score was 5 or more, intravenous fentanyl 25 µg was given and repeated if required.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Fentanyl consumption at 2 hours postoperatively; Group 1: mean 1.25 Micrograms (SD 5.534); n=60, Group 2: mean 0 Micrograms (SD 0); n=30
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Ramsay Sedation score at 6 hours postoperatively; Group 1: mean 2 (SD 0); n=60, Group 2: mean 2 (SD 0); n=60; Ramsay Sedation score 0-6 Top=High is poor outcome

Study	Balaban 2012[69]
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Nausea at postoperatively; Group 1: 6/60, Group 2: 5/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 6/60, Group 2: 9/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0 - Actual outcome: Pruritis at postoperatively; Group 1: 1/60, Group 2: 3/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Urinary Retention at postoperatively; Group 1: 0/60, Group 2: 1/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Somnolence at postoperatively; Group 1: 0/60, Group 2: 1/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Behdad 2012[90]
Study type	Systematic Review
Number of studies (number of participants)	(n=61)
Countries and setting	Conducted in Iran; Setting: Department of Gynaecology, Shahid Sadoughi University of Medical Sciences, Iran
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Study	Behdad 2012[90]
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients had to be at least 20 years old and over 40 kg of weight.
Exclusion criteria	All patients with a history of sensitivity to opioids, asthma, renal failure, peptic ulcer, mental diseases, cardiovascular diseases, body mass index (BMI) more than 35 and previous surgery with more than 2.5 hours duration were excluded from the study.
Recruitment/selection of patients	patients who were for total abdominal hysterectomy under general anaesthesia
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 45.86 ± 4.06; Placebo: 48.16 ± 4.48. Gender (M:F): not specified. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 45.86 ± 4.06; Placebo: 48.16 ± 4.48). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (total abdominal hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Patients in the study population got 100 mg gabapentin the night before surgery and 300 mg gabapentin (one capsule) two hours before surgery. . Duration preoperatively. Concurrent medication/care: Opioids used as rescue medication, type of opioid used not specified.. Indirectness: No indirectness (n=31) Intervention 2: Opioid only. In the Placebo group, patients got one capsule of multi-vitamin two hours before surgery.. Duration preoperatively. Concurrent medication/care: Opioids used as rescue medication, type of opioid used not specified.. Indirectness: No indirectness
Funding	Academic or government funding
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Clarke 2013[188]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)

Study	Clarke 2013[188]
Countries and setting	Conducted in Canada; Setting: Toronto General Hospital, University Health Network
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I, II, or III and scheduled for non-cardiac surgery with a pre-operative anxiety score of greater than or equal to 5/10 on a NRS.
Exclusion criteria	the inability to understand English or to provide informed consent; a known allergy to gabapentin; abnormal liver or renal function; known HIV, hepatitis B, or hepatitis C infection; severe mental illness; and diabetic patients on insulin or with impaired renal function (creatinine level[106 lmol□L-1). Subjects currently taking gabapentin or pregabalin, those who were pregnant or breastfeeding, or those with a history of drug or alcohol abuse were also excluded.
Recruitment/selection of patients	Patients scheduled for non-cardiac surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 41.6±6.6; Placebo: 41.8±6.8. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 41.6±6.6; Placebo: 41.8±6.8). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I, II or III). 3. Type of surgery: Not stated / Unclear (General; Gynaecological; Plastics; Ear, Nose & Throat).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Gabapentin 1,200 mg administered 2.5 hours before surgery. Duration preoperatively. Concurrent medication/care: Results show patients received Fentanyl (µg) Morphine (mg) but not dosage information given.. Indirectness: No indirectness (n=25) Intervention 2: Opioid only. Placebo administered 2.5 hours before surgery. Duration preoperatively. Concurrent medication/care: Results show patients received Fentanyl (µg) Morphine (mg) but not dosage information given.. Indirectness: No indirectness
Funding	Funding not stated

Study	Clarke 2013[188]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain score 2 hours at 2 hours postoperatively; Median (IQR): Gabapentin: 0(0-1); Placebo: 0(0-2) Numerical Rating Scale 0-10 Top=High is poor outcome; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Did not complete post operative follow up; Group 2 Number missing: 3, Reason: Did not complete post operative follow up Protocol outcome 2: Amount of additional medication use (< 6 hours post op) - Actual outcome: Fentanyl Consumption at 1 hour postoperatively; Group 1: mean 8 µg - micrograms (SD 19); n=22, Group 2: mean 25.7 µg - micrograms (SD 36.3); n=22; Comments: p value 0.05 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Did not complete post operative follow up; Group 2 Number missing: 3, Reason: Did not complete post operative follow up - Actual outcome: Morphine Consumption at 1 hour postoperatively; Group 1: mean 0.8 Micrograms (SD 2.1); n=22, Group 2: mean 1.3 Micrograms (SD 2.8); n=22; Comments: p value 0.53 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Did not complete post operative follow up; Group 2 Number missing: 3, Reason: Did not complete post operative follow up Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Sedation score at 2 hours postoperatively; Median (IQR): Gabapentin: 7(5-8); Placebo: 5(2-8) Numerical Rating Scale 0-10 Top=High is poor outcome; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Did not complete post operative follow up; Group 2 Number missing: 3, Reason: Did not complete post operative follow up Protocol outcome 4: Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) - Actual outcome: Anxiety Score (NRS) at 2 hours postoperatively; Median (IQR): Gabapentin: 2.5 [1.0-4.0]; Placebo: 4.0 [2.0- 5.0] Numerical rating scale 0-10 Top=High is poor outcome; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Did not complete post operative follow up; Group 2 Number missing: 3, Reason: Did not complete post operative follow up - Actual outcome: McGill Pain Questionnaire at 2 hours postoperatively; Median (IQR):: Gabapentin: 0.6 [0.1-1.2]; Placebo: 0.5 [0.1-1.2] McGill Pain Questionnaire 0-230 Top=High is poor outcome;	

Study	Clarke 2013[188]
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Did not complete post operative follow up; Group 2 Number missing: 3, Reason: Did not complete post operative follow up	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Dierking 2004[242]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in Denmark; Setting: The Department of Gynaecology, Herning Central Hospital, and The Department of Gynaecology, Herlev University Hospital: Denmark
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Women aged 18—75 years, scheduled for elective total or subtotal abdominal hysterectomy with or without salpingo-oophorectomy
Exclusion criteria	Patients were not included if they were unable to cooperate, had known allergy to gabapentin or morphine, a history of drug or alcohol abuse, chronic pain or daily intake of analgesics or corticosteroids, diabetes or impaired kidney function. Patients with an intake of NSAIDs or paracetamol 24 h, or an intake of antacids 48 h prior to operation were also excluded from the study.
Recruitment/selection of patients	scheduled for elective total or subtotal abdominal hysterectomy with or without salpingo-oophorectomy
Age, gender and ethnicity	Age - Median (range): Gabapentin: 46 (26—73); Placebo: 48 (36—62). Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 46 (26—73); Placebo: 48 (36—62)). 2. American Society of

Study	Dierking 2004[242]
	Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (abdominal hysterectomy with or without salpingo-oophorectomy).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. oral gabapentin 1200 mg 1 h before surgery, followed by oral gabapentin 600 mg 8, 16 and 24 h after the initial dose.. Duration peroperatively. Concurrent medication/care: Postoperative pain treatment consisted of patient controlled intravenous morphine (PCA) bolus 2.5 mg, lock-out time 10 min. Additional morphine 2.5 mg intravenously was administered by a nurse observer, if requested by the patient, during the first postoperative hour. Ondansetron 4 mg intravenously was administered on patient request. No other medications were administered during the 24-h observation period.. Indirectness: No indirectness (n=40) Intervention 2: Opioid only. receive oral placebo 1 h before surgery, followed by placebo 8, 16 and 24 h after the initial dose.. Duration perioperatively. Concurrent medication/care: Postoperative pain treatment consisted of patient controlled intravenous morphine (PCA) bolus 2.5 mg, lock-out time 10 min. Additional morphine 2.5 mg intravenously was administered by a nurse observer, if requested by the patient, during the first postoperative hour. Ondansetron 4 mg intravenously was administered on patient request. No other medications were administered during the 24-h observation period.. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Study medication provided by Pzifer, Denmark)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at 24 hours postoperatively; Group 1: 12/39, Group 2: 11/32
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Incorrect connection to PCA-device (n = 1); Group 2 Number missing: 8, Reason: Received medication not described in protocol (n = 3)
Patient wished to withdraw after inclusion (n = 3)
Changed surgical procedure (n = 1)
Developed neurological symptoms (n = 1)
- Actual outcome: Vomiting at 24 hours postoperatively; Group 1: 18/39, Group 2: 15/32
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Incorrect connection to PCA-device (n = 1); Group 2 Number missing: 8, Reason: Received medication not described in protocol (n = 3)
Patient wished to withdraw after inclusion (n = 3)

Study	Dierking 2004[242]
	Changed surgical procedure (n = 1) Developed neurological symptoms (n = 1) - Actual outcome: Dizziness at 24 hours postoperatively; Group 1: 23/39, Group 2: 15/32 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Incorrect connection to PCA-device (n = 1); Group 2 Number missing: 8, Reason: Received medication not described in protocol (n = 3) Patient wished to withdraw after inclusion (n = 3) Changed surgical procedure (n = 1) Developed neurological symptoms (n = 1) - Actual outcome: Somnolence at 24 hours postoperatively; Median (IQR): Gabapentin: 0 (0-0); Placebo: 0 (0-0)); Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Incorrect connection to PCA-device (n = 1); Group 2 Number missing: 8, Reason: Received medication not described in protocol (n = 3) Patient wished to withdraw after inclusion (n = 3) Changed surgical procedure (n = 1) Developed neurological symptoms (n = 1) - Actual outcome: Somnolence at < 6 hours postoperatively; Median (IQR): Gabapentin: 1 (0-1.5); Placebo: 0.5 (0-1)); Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Incorrect connection to PCA-device (n = 1); Group 2 Number missing: 8, Reason: Received medication not described in protocol (n = 3) Patient wished to withdraw after inclusion (n = 3) Changed surgical procedure (n = 1) Developed neurological symptoms (n = 1)
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Dirks 2002[245]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=70)
Countries and setting	Conducted in Denmark
Line of therapy	1st line

Study	Dirks 2002[245]
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Women aged 18–75 yr who were scheduled for unilateral radical mastectomy with axillary dissection were eligible for the study.
Exclusion criteria	Patients were not included if they were unable to cooperate, had known allergy to gabapentin or morphine, a history of drug or alcohol abuse, chronic pain or daily intake of analgesics or corticosteroids, diabetes, or impaired kidney function. Patients with an intake of NSAIDs or paracetamol 24 h prior to operation or an intake of antacids 48 h prior to operation were also excluded from the study.
Recruitment/selection of patients	scheduled for unilateral radical mastectomy with axillary dissection
Age, gender and ethnicity	Age - Mean (range): Gabapentin: 61 (54–67); Placebo: 60 (52–69). Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: >60 years (Gabapentin: 61 (54–67); Placebo: 60 (52–69)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (unilateral radical mastectomy with axillary dissection).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 1,200 mg oral gabapentin 1 h before surgery and 0.125 mg sublingual triazolam. Duration preoperative. Concurrent medication/care: patient-controlled intravenous morphine, 2.5-mg bolus, 10 min lock-out time. Additional morphine, 2.5 mg intravenously, was administered by a nurse observer, if requested by the patient, during the lock-out period. Ondansetron, 4 mg intravenously, was administered on patient request. No other medications were administered during the 4-h observation period.. Indirectness: No indirectness (n=35) Intervention 2: Opioid only. Identical placebo 1 h before surgery and 0.125 mg sublingual triazolam. Duration preoperative. Concurrent medication/care: patient-controlled intravenous morphine, 2.5-mg bolus, 10 min lock-out time. Additional morphine, 2.5 mg intravenously, was administered by a nurse observer, if requested by the patient, during the lock-out period. Ondansetron, 4 mg intravenously, was administered on patient request. No other medications were administered during the 4-h observation period.. Indirectness: No indirectness
Funding	Funding not stated

Study	Dirks 2002[245]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain scores 4 hours at ≤ 4 hours postoperatively; Median (IQR): Gabapetin: 7 (1–18) mm ; Placebo: 12 (9–30) mm visual analogue scale 0-100 Top=High is poor outcome, Comments: P = 0.084;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: unable to swallow, bleeding, incorrect connection to PCA, incorrect medication ; Group 2 Number missing: 1, Reason: incorrect connection to PCA

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Total morphine consumption at ≤ 4 hours postoperatively; Median (IQR): Gabapentin: 15 (10–19) mg; Placebo: 29 (21–23) mg milligrams);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: unable to swallow, bleeding, incorrect connection to PCA, incorrect medication ; Group 2 Number missing: 1, Reason: incorrect connection to PCA

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at ≤ 4 hours postoperatively; Group 1: 2/31, Group 2: 3/34
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: unable to swallow, bleeding, incorrect connection to PCA, incorrect medication ; Group 2 Number missing: 1, Reason: incorrect connection to PCA
- Actual outcome: Somnolence at ≤ 4 hours postoperatively; Group 1: 20/31, Group 2: 22/34
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: unable to swallow, bleeding, incorrect connection to PCA, incorrect medication ; Group 2 Number missing: 1, Reason: incorrect connection to PCA
- Actual outcome: Dizziness at ≤ 4 hours postoperatively; Group 1: 8/31, Group 2: 11/34
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: unable to swallow, bleeding, incorrect connection to PCA, incorrect medication ; Group 2 Number missing: 1, Reason: incorrect connection to PCA
- Actual outcome: Headache at ≤ 4 hours postoperatively; Group 1: 1/31, Group 2: 1/34
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: unable to swallow, bleeding, incorrect connection to PCA, incorrect medication ; Group 2 Number missing: 1, Reason: incorrect connection to PCA
- Actual outcome: light headed at ≤ 4 hours postoperatively; Group 1: 16/31, Group 2: 16/34
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Dirks 2002[245]
- Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: unable to swallow, bleeding, incorrect connection to PCA, incorrect medication ; Group 2 Number missing: 1, Reason: incorrect connection to PCA	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Durmus 2007[257]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=75)
Countries and setting	Conducted in Turkey; Setting: Department of Anaesthesiology, Inonu University, School of Medicine, Malatya, Turkey
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA physical status I–II patients aged 18 years orabove who were scheduled for elective totalabdom-inal hysterectomy under general anaesthesia in theGynaecology and Obstetrics Department who couldoperate a patient-controlled analgesia (PCA) device
Exclusion criteria	history of cardiovascular, respiratory, renal or hepatic disease, psychiatric disorders, asthma, chronic pain syndromes or drug and alcohol abuse. Patients receiving regular opioids or drugs with known analgesic properties within 2 h prior to surgery were also excluded
Recruitment/selection of patients	scheduled for elective total abdominal hysterectomy under general anaesthesia

Study	Durmus 2007[257]
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 48 ± 7; Placebo: 48 ± 7 . Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 48 ± 7; Placebo: 48 ± 7). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I 33; ASA II 17). 3. Type of surgery: gynae-oncology (abdominal hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Gabapentin 1200mg 1 hour prior to the induction of anaesthesia . Duration preoperatively. Concurrent medication/care: All patients received PCA with intravenous morphine and were followed for 24 h by the study nurses who were blinded to the study protocol. After administration of5 mg morphine over 30 min, starting 15 min before the estimated time of completion of surgery, the PCA device was set to deliver 2 mg of morphine with a lock-out of 15min and 4 h limit of 35 mg, and no continuous infusion. If analgesia was felt to be in adequate at any time during the study period, the lockout time was shortened to 5 min. . Indirectness: No indirectness (n=25) Intervention 2: Opioid only. Placebo capsules 1 hour before the induction of anesthesia. Duration preoperatively. Concurrent medication/care: All patients received PCA with intravenous morphine and were followed for 24 h by the study nurses who were blinded to the study protocol. After administration of5 mg morphine over 30 min, starting 15 min before the estimated time of completion of surgery, the PCA device was set to deliver 2 mg of morphine with a lock-out of 15min and 4 h limit of 35 mg, and no continuous infusion. If analgesia was felt to be in adequate at any time during the study period, the lockout time was shortened to 5 min. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at Postoperatively; Group 1: 7/25, Group 2: 29/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Durmus 2007[257]
- Actual outcome: Vomiting at Postoperatively; Group 1: 3/25, Group 2: 6/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pruritis at Postoperatively; Group 1: 1/25, Group 2: 2/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Headache at Postoperatively; Group 1: 1/25, Group 2: 1/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Eidy 2017[263]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=108)
Countries and setting	Conducted in Iran; Setting: Trauma Research Center, Kashan University of Medical Sciences, Matini Hospital, Amirkabir Avenue, Kashan 8719674591, Iran
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged between 20 - 60 ASA I or II undergoing laparoscopic cholecystectomy
Exclusion criteria	Not specified
Recruitment/selection of patients	Patients undergoing laparoscopic cholecystectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin:44.0 ± 9.5; Pregabalin:43.1 ± 1.1; Placebo: 45.3 ± 9.3. Gender (M:F): 85/23. Ethnicity: NA

Study	Eidy 2017[263]
Further population details	1. Age: <60 years (Gabapentin:44.0 ± 9.5; Pregabalin:43.1 ± 1.1; Placebo: 45.3 ± 9.3). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (Laproscopic cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Patients were given Gabapentin 800mg one hour before surgery given 1 hour before surgery. Duration preoperatively. Concurrent medication/care: In the cases where the patient felt pain in the recovery room, if the pain score was more than 4, the patient received 25 mg of intravenous pethidine. After patients were transferred to the ward, analgesia was administered by pethidine via patient-controlled analgesia.. Indirectness: No indirectness (n=36) Intervention 2: Opioid plus neuropathic nerve stabiliser - Pregabalin. Patients were given 150mg of pregabalin orally, one hour before surgery. Duration preoperatively. Concurrent medication/care: In the cases where the patient felt pain in the recovery room, if the pain score was more than 4, the patient received 25 mg of intravenous pethidine. After patients were transferred to the ward, analgesia was administered by pethidine via patient-controlled analgesia.. Indirectness: No indirectness (n=36) Intervention 3: Opioid only. Patients in the placebo group did not receive Pregabalin or Gabapentin preoperatively.. Duration preoperatively. Concurrent medication/care: In the cases where the patient felt pain in the recovery room, if the pain score was more than 4, the patient received 25 mg of intravenous pethidine. After patients were transferred to the ward, analgesia was administered by pethidine via patient-controlled analgesia.. Indirectness: No indirectness
Funding	Academic or government funding (supported by the Deputy of Research, Kashan University of Medical Sciences (grant number: 90002).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PREGABALIN

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Pethidine consumption at 6 hours postoperatively ; Group 1: mean 27.8 milligrams (SD 3.5); n=36, Group 2: mean 23.7 milligrams (SD 3.6); n=36
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Pethidine consumption at 24 hours postoperatively ; Group 1: mean 79.9 milligrams (SD 1.8); n=36, Group 2: mean 89.2 milligrams (SD 2.8); n=36

Study	Eidy 2017[263]
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Nausea at 24 hours postoperatively ; Group 1: 7/36, Group 2: 10/36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at 24 hours postoperatively ; Group 1: 16/36, Group 2: 13/36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO Protocol outcome 1: Amount of additional medication use (< 6 hours post op) - Actual outcome: Pethidine consumption at 6 hours postoperatively ; Group 1: mean 27.8 milligrams (SD 3.5); n=36, Group 2: mean 30.3 milligrams (SD 23.7); n=36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Pethidine consumption at 24 hours postoperatively ; Group 1: mean 79.9 milligrams (SD 1.8); n=36, Group 2: mean 89.2 milligrams (SD 2.8); n=36 Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Nausea at 24 hours postoperatively ; Group 1: 7/36, Group 2: 11/36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at 24 hours postoperatively ; Group 1: 16/36, Group 2: 24/36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO Protocol outcome 1: Amount of additional medication use (< 6 hours post op)	

Study	Eidy 2017[263]
- Actual outcome: Pethidine consumption at 6 hours postoperatively ; Group 1: mean 23.7 milligrams (SD 3.6); n=36, Group 2: mean 30.6 milligrams (SD 1); n=36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Pethidine consumption at 24 hours postoperatively ; Group 1: mean 78.2 milligrams (SD 3.5); n=36, Group 2: mean 89.2 milligrams (SD 2.8); n=36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Nausea at 24 hours postoperatively ; Group 1: 10/36, Group 2: 11/36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at 24 hours postoperatively ; Group 1: 13/36, Group 2: 24/36 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Eman 2014[272]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Turkey; Setting: Tertiary Hospital, Turkey
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Study	Eman 2014[272]
Subgroup analysis within study	Not applicable
Inclusion criteria	18-60 yaars, ASA I-II scheduled for total abdominal hysterectomy surgery under general anesthesia
Exclusion criteria	Patients with known renal, hepatic, pulmonary or cardiovascular system's problems, drug or alcohol addiction, history of allergy and obese patients were excluded from the study
Recruitment/selection of patients	scheduled for total abdominal hysterectomy surgery under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 43.45 ± 11.56; Placebo: 42.15 ± 11.12. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 43.45 ± 11.56; Placebo: 42.15 ± 11.12). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: gynae-oncology (total abdominal hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. 150 mg of oral pregabalin given 60 minutes prior to the surgery. Duration preoperatively . Concurrent medication/care: when the Aldrete recovery score (ARS) (10) reached 9, morphine infusion was started using the patient-controlled analgesia method. Morphine 50 mg was added into 100 ml of normal saline. Initial settings of the Patient-Controlled Analgesia (PCA) device were as follows: bolus dose 1 mg, lockout interval 10 minutes and a 4-hour limit 40 mg. The time first bolus used in the PCA system was recorded as the first analgesic requirement time.. Indirectness: No indirectness (n=20) Intervention 2: Opioid only. oral placebo capsule given 60 minutes prior to the surgery.. Duration preoperatively. Concurrent medication/care: when the Aldrete recovery score (ARS) (10) reached 9, morphine infusion was started using the patient-controlled analgesia method. Morphine 50 mg was added into 100 ml of normal saline. Initial settings of the Patient-Controlled Analgesia (PCA) device were as follows: bolus dose 1 mg, lockout interval 10 minutes and a 4-hour limit 40 mg. The time first bolus used in the PCA system was recorded as the first analgesic requirement time.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Morphine Consumption 4 hours at 4 hours postoperatively; Group 1: mean 6.9 milligrams (SD 2.5); n=20, Group 2: mean 8.9 milligrams (SD 1.4); n=20; Comments: p value 0.08
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Study	Eman 2014[272]
Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Morphine Consumption 24 hours at 24 hours postoperatively; Group 1: mean 19.9 milligrams (SD 6.5); n=20, Group 2: mean 35.1 milligrams (SD 5.5); n=20; Comments: p value 0.0001 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Nausea at 24 hours postoperatively; Group 1: 3/20, Group 2: 4/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Pruritus at 24 hours postoperatively; Group 1: 1/20, Group 2: 0/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Ghafari 2009[325]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=99)
Countries and setting	Conducted in Iran; Setting: Tehran University of Medical Sciences, Iran
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II scheduled for elective total abdominal hysterectomy and salpingoopherectomy and under general anesthesia, ≥20 years old who were over 40kg and had no psychologic problem could participate in this

Study	Ghafari 2009[325]
	protocol
Exclusion criteria	Patients with opioid allergy, asthma, renal insufficiency, history of peptic ulcer or bleeding diathesis, mental impairment, chronic pain, cardiovascular, hepatic or renal diseases, BMI > 35, patients who received analgesic or opioids 48h before surgery, drug or alcoholic abusers and surgery time over 2.5h all were excluded.
Recruitment/selection of patients	scheduled for elective total abdominal hysterectomy and salpingoopherectomy and under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): gabapentin: 44.65 ± 1.31; Placebo: 44.55 ± 1.12. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (gabapentin: 44.65 ± 1.31; Placebo: 44.55 ± 1.12). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: gynae-oncology (total abdominal hysterectomy and salpingoopherectomy).
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 300mg Gabapentin at 10pm the night before surgery and 1 hour before surgery. Duration preoperative administration. Concurrent medication/care: Postoperative IV analgesia was provided through a PCA. The PCA pump was loaded with morphine hydrochloride 1mg/mL diluted in 0.9% NaCl and was programmed to delivery on request a 1mg morphine bolus with a lock out period of 7 minutes between 2 consecutive boluses. No other analgesia was administered for the patients. . Indirectness: No indirectness (n=33) Intervention 2: Opioid only. Placebo given at 10pm the night before surgery and 1 hour before surgery. Duration preoperatively. Concurrent medication/care: Postoperative IV analgesia was provided through a PCA. The PCA pump was loaded with morphine hydrochloride 1mg/mL diluted in 0.9% NaCl and was programmed to delivery on request a 1mg morphine bolus with a lock out period of 7 minutes between 2 consecutive boluses. No other analgesia was administered for the patients. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain scores 6 hours postoperatively at < 6 hours postoperatively; Group 1: mean 4.25 pain score (SD 0.35); n=33, Group 2: mean 5.81 pain score (SD 0.4); n=33; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Ghafari 2009[325]
	Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: pain scores 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 1.81 pain score (SD 0.3); n=33, Group 2: mean 3.48 pain score (SD 0.4); n=33; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: total morphine consumption at 24 hours postoperatively; Group 1: mean 15.78 milligrams (SD 1.15); n=33, Group 2: mean 26.94 milligrams (SD 2.28); n=33 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0 Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Nausea at postoperatively; Group 1: 5/33, Group 2: 7/33 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 4/33, Group 2: 9/33 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Dizziness at postoperatively; Group 1: 2/33, Group 2: 2/33 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Somnolance at postoperatively; Group 1: 2/33, Group 2: 3/33 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pruritis at postoperatively; Group 1: 2/33, Group 2: 4/33 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Hanoura 2018[380]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Egypt; Setting: Department of Cardiothoracic Surgery, Faculty of Medicine, AL-Azhar University, Cairo, Egypt.
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	patients undergoing CABG surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 61.7± 7.6; Pregabalin: 61± 7.1; Placebo: 59.5± 7.8. Gender (M:F): Define. Ethnicity: NA
Further population details	1. Age: >60 years (Gabapentin: 61.7± 7.6; Pregabalin: 61± 7.1; Placebo: 59.5± 7.8). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not stated / Unclear (Coronary artery bypass graft).
Indirectness of population	--
Interventions	(n=20) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. patients were given 600mg gabapentin (Gabapentin group). All groups received their medication 2 h prior to surgery. Duration preoperative. Concurrent medication/care: Post-extubation pain was controlled with intravenous PCA morphine 2 mg, with a lockout time of 10 min. Rescue analgesia included intravenous paracetamol (1 g) with maximum 4 g over 24 h or intravenous 3mg morphine which can be increased up to 8mg was given.. Indirectness: No indirectness (n=20) Intervention 2: Opioid plus neuropathic nerve stabiliser - Pregabalin. Patients were given 150mg pregabalin (Pregabalin group). All groups received their medication 2 h prior to surgery. Duration preoperative. Concurrent medication/care: Post-extubation pain was controlled with intravenous PCA morphine 2 mg, with a lockout time of 10 min. Rescue analgesia included intravenous paracetamol (1 g) with maximum 4 g over 24 h or intravenous 3mg morphine which can be increased up to 8mg was given.. Indirectness: No indirectness

	(n=20) Intervention 3: Opioid only. placebo group received identical capsule (as pregabalin and gabapentin). All groups received their medication 2 h prior to surgery. Duration preoperative. Concurrent medication/care: Post-extubation pain was controlled with intravenous PCA morphine 2 mg, with a lockout time of 10 min. Rescue analgesia included intravenous paracetamol (1 g) with maximum 4 g over 24 h or intravenous 3mg morphine which can be increased up to 8mg was given.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PREGABALIN

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at 6 hours postoperatively; Group 1: mean 1 pain score (SD 0.6); n=19, Group 2: mean 1 pain score (SD 0.5); n=18; NRS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: pain score at 24 hours postoperatively; Group 1: mean 1.3 pain score (SD 0.7); n=19, Group 2: mean 1.2 pain score (SD 0.8); n=18; NRS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Additional morphine at 24 hours postoperative; Group 1: mean 27.1 milligrams (SD 5.1); n=1, Group 2: mean 22.4 milligrams (SD 6); n=18
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at 24 hours postoperatively; Group 1: 6/19, Group 2: 4/18
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2
- Actual outcome: Vomiting at 24 hours postoperatively; Group 1: 3/19, Group 2: 2/18
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2
- Actual outcome: Somnolence at 24 hours postoperatively; Group 1: 4/19, Group 2: 4/18

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2
- Actual outcome: Dizziness at 24 hours postoperatively; Group 1: 4/19, Group 2: 3/18
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 5: Length of hospital stay
- Actual outcome: Length of stay at postoperative; Group 1: mean 6.8 days (SD 1.9); n=19, Group 2: mean 7.3 days (SD 3.2); n=18
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at 6 hours postoperatively; Group 1: mean 1.2 (SD 0.8); n=19, Group 2: mean 1.3 (SD 0.7); n=19; NRS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: pain score at 24 hours postoperatively; Group 1: mean 1.6 (SD 0.7); n=19, Group 2: mean 1.6 (SD 0.9); n=19; NRS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Additional morphine at 24 hours postoperative; Group 1: mean 27.1 milligrams (SD 5.1); n=19, Group 2: mean 31 milligrams (SD 5.1); n=19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at 24 hours postoperatively; Group 1: 6/19, Group 2: 2/19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome: Vomiting at 24 hours postoperatively; Group 1: 3/19, Group 2: 1/19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness

of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome: Somnolence at 24 hours postoperatively; Group 1: 4/19, Group 2: 0/19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome: Dizziness at 24 hours postoperatively; Group 1: 4/19, Group 2: 0/19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 5: Length of hospital stay
- Actual outcome: Length of stay at postoperative; Group 1: mean 6.8 days (SD 1.9); n=19, Group 2: mean 7.6 days (SD 2.8); n=19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at 6 hours postoperatively; Group 1: mean 1 (SD 0.5); n=19, Group 2: mean 1.3 (SD 0.7); n=19; NRS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: pain score at 24 hours postoperatively; Group 1: mean 1.2 (SD 0.8); n=19, Group 2: mean 1.26 (SD 0.7); n=19; NRS 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Additional morphine at 24 hours postoperative; Group 1: mean 22.4 (SD 6); n=18, Group 2: mean 31 (SD 5.1); n=19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at 24 hours postoperatively; Group 1: 4/18, Group 2: 2/19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1
- Actual outcome: Vomiting at 24 hours postoperatively; Group 1: 2/18, Group 2: 1/19

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 - Actual outcome: Somnolence at 24 hours postoperatively; Group 1: 4/18, Group 2: 0/19 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 - Actual outcome: Dizziness at 24 hours postoperatively; Group 1: 3/18, Group 2: 0/19 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 Protocol outcome 5: Length of hospital stay - Actual outcome: Length of stay at postoperative; Group 1: mean 7.3 days (SD 3.2); n=18, Group 2: mean 7.6 days (SD 3.8); n=19 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Hassani 2015[385]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Iran; Setting: Hazrat Rasul Hospital
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	candidates for the LGBP surgery, age > 18 years, ASA class II or I, morbid obesity (body mass index [BMI] ≥ 40 kg/m2)
Exclusion criteria	cardio-vascular and respiratory diseases, frequent headaches, dizziness, drug and/or alcohol abuse, use of daily analgesia 48 hours before the surgery, renal failure, and liver dysfunction

Recruitment/selection of patients	individuals who underwent Laparoscopic Gastric Bypass during 2012-2013.
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 33.4 ± 5.7; Placebo: 35.3 ± 9.2. Gender (M:F): 27/33. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 33.4 ± 5.7; Placebo: 35.3 ± 9.2). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: lower and upper GI (Laparoscopic Gastric Bypass).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Gabapentin group received 100 mg of oral gabapentin one hour before induction of anesthesia. In the operating room, a 10-mg capsule of gabapentin was given to gabapentin group. Duration Intraoperative administration. Concurrent medication/care: If the pain score was > 4, analgesia (IV narcotic opiates) was administered.. Indirectness: No indirectness (n=30) Intervention 2: Opioid only. placebo group received identical-to-gabapentin placebo capsules one hour before induction of anesthesia. In the operating room, a placebo capsule was given to this group.. Duration Intraoperative administration. Concurrent medication/care: If the pain score was > 4, analgesia (IV narcotic opiates) was administered.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain ≤ 6 hours at ≤ 6 hours postoperatively; Group 1: mean 2.1 pain score (SD 0.3); n=30, Group 2: mean 2.3 pain score (SD 0.5); n=30; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.1
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Dose of Consumed Opioid, mg at Postoperatively; Group 1: mean 20.7 milligrams (SD 13.7); n=30, Group 2: mean 32.5 milligrams (SD 14.1); n=30; Comments: p value 0.08
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea & Vomiting at Postoperatively; Group 1: 3/30, Group 2: 10/30; Comments: 0.028

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing:0 - Actual outcome: Headache at Postoperatively; Group 1: 1/30, Group 2: 3/30; Comments: p value 0.3 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Hetta 2016[396]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=120)
Countries and setting	Conducted in Egypt; Setting: South Egypt Cancer Institute, Assiut University, Assiut, Egypt
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I and II, scheduled for unilateralMRM with axillary evacuation
Exclusion criteria	patientswith a known allergy to pregabalin or morphine, pregnancy or breastfeeding, a history of drug or alcohol abuse, patients with impaired kidney or liver functions, patients with chronic pain or regularly receiving analgesics, and previous or current use of gabapentinoids
Recruitment/selection of patients	scheduled for unilateralMRM with axillary evacuation were consecutively enrolled
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 47.61 ± 7.27 ; Placebo: 47.4 ± 7.4. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 47.61 ± 7.27 ; Placebo: 47.4 ± 7.4). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 80 ASA II: 31). 3. Type of surgery: Not applicable (modified radical mastectomy).
Indirectness of population	--

Interventions	(n=90) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. patients received orally 2 hours before surgery the study medication: pregabalin (75 mg, 150mg, 300mg).. Duration Preoperatively. Concurrent medication/care: PCA with an initial morphine bolus of 0.1 mg/kg once the patient requested analgesia, followed by 1-mg boluses on demand without background infusion with a lockout period of 5 minutes. . Indirectness: No indirectness (n=30) Intervention 2: Opioid only. patients received orally 2 hours before surgery the study medication: placebo capsule. Duration preoperatively. Concurrent medication/care: PCA with an initial morphine bolus of 0.1 mg/kg once the patient requested analgesia, followed by 1-mg boluses on demand without background infusion with a lockout period of 5 minutes. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain scores 2 - 4 hours at ≤4 hours postoperatively; median (IQR): Pregabalin: (75mg) 2 (1-2), (150mg) 1 (1-2), (300mg) 1 (0-2); Placebo: 2 (1-2) pain score visual analogue scale 0-10 Top=High is poor outcome; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0 Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: Pain scores 24 hours at 24 hours postoperatively; Median (IQR) : Pregabalin: (75mg) 1.5 (1-2), (150mg) 1 (1-2), (300mg) 1 (0-2); Placebo: 2 (1-2) pain score visual analogue scale 0-10 Top=High is poor outcome; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Hosseini 2015[406]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	(n=88)
Countries and setting	Conducted in Iran; Setting: Tehran University of Medical Sciences, Iran
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II scheduled for laparoscopic cholecystectomy
Exclusion criteria	Patients with history of congestive heart failure, valvular heart disease, renal or hepatic failure, psychiatric disorders (physical symptoms, depression, loss of energy), drug abuse, uncontrolled hypertension and also patients with language and communication problems were not enrolled in the study
Recruitment/selection of patients	scheduled for laparoscopic cholecystectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 40.50 ± 8.38 ; Placebo: 38.14 ± 10.80. Gender (M:F): not specified . Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 40.50 ± 8.38 ; Placebo: 38.14 ± 10.80). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (laparoscopic cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Patients given 600mg Gabapentin 2 hours before surgery. Duration preoperatively. Concurrent medication/care: PCA pump containing morphine at a concentration of 0.5 mg/ml was connected to the patients. Device setting was adjusted as "basic infusion of 2 ml/h, demand dose of 1 ml and lockout Interval of 15 minutes". PCA pump was connected to the patients during the first 24 hours after surgery. . Indirectness: No indirectness (n=22) Intervention 2: Opioid only. Placebo given 2 hours before surgery. Duration preoperatively. Concurrent medication/care: PCA pump containing morphine at a concentration of 0.5 mg/ml was connected to the patients. Device setting was adjusted as "basic infusion of 2 ml/h, demand dose of 1 ml and lockout Interval of 15 minutes". PCA pump was connected to the patients during the first 24 hours after surgery. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain scores 6 hours at 6 hours postoperatively; Group 1: mean 1.64 pain score (SD 1.02); n=22, Group 2: mean 3.09 pain score (SD 1.01); n=22; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: Pain scores 12 hours at 12 hours postoperatively; Group 1: mean 0.77 pain score (SD 0.57); n=22, Group 2: mean 1.36 pain score (SD 1.04); n=22; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing:0 Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Morphine consumption at 24 hours postoperatively; Group 1: mean 65.91 milligrams (SD 11.81); n=22, Group 2: mean 78.41 milligrams (SD 13.3); n=22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Kerrick 1993[501]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=28)
Countries and setting	Conducted in USA; Setting: University of Utah Health Sciences Centre, Utah, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Undergoing elective knee or hip arthroplasty , ability to comprehend the rating scales used to assess pain, global sense of well being, and sleep quality, as well as understand the PCA device and agree to the use of this modality for pain control.
Exclusion criteria	1:Documented adverse reaction to tri-cyclic antidepressants or unusual opioid reactions; 2: history of chronic or daily (within 1 week of admission) use of neuroleptic, antidepressant, opioid, anxiolytic or hypnotic medications; 3: diagnosed chronic pain syndrome (pain duration longer than 6 months and not including pain directly attributable to the affected joint); 4: cardiac arrhythmia, history of myocardial infarction within the past year, angina pectoris and 5: age less than 18 or greater than 79 years.
Recruitment/selection of patients	Scheduled elective knee or hip arthroplasty
Age, gender and ethnicity	Age - Mean (SD): Amitriptyline: 64.2 ± 11.2 ; Placebo: 59.4 ± 12.0. Gender (M:F): 17/11. Ethnicity: NA
Further population details	1. Age: >60 years (Amitriptyline: 64.2 ± 11.2 ; Placebo: 59.4 ± 12.0). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: ortho/large joint replacement (elective knee or hip arthroplasty).
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Opioid plus neuropathic nerve stabiliser - Amitriptyline. 50mg of amitriptyline orally in an extemporaneously compounded liquid for for 3 consecutive evenings as a supplement to PCA (opioid) therapy. . Duration 73 hours postoperatively. Concurrent medication/care: PCA drug meperidine (3mg/ml) or Morphine sulfate 0.3mg/ml. Indirectness: No indirectness (n=14) Intervention 2: Opioid only. The palcebo groups received the placebo which was the liquid vehicle without amitriptyline. Duration 72 hours postoperatively. Concurrent medication/care: PCA drug meperidine (3mg/ml) or Morphine sulfate 0.3mg/ml. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMITRIPTYLINE versus PLACEBO

Protocol outcome 1: Length of hospital stay
- Actual outcome: Number of days in hospital at admission to discharge; Group 1: mean 9.4 days (SD 4); n=12, Group 2: mean 7.9 days (SD 2); n=12
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Protocol violation or withdrawal ; Group 2 Number missing: 2, Reason: Protocol violation or withdrawal

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Hospital readmission

Study	**Khademi 2010[502]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Iran; Setting: Department of Anesthesiology, Fasa University of Medical Sciences, Fasa , Iran
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	scheduled for elective open cholecystectomy
Exclusion criteria	Patients with a BMI > 30; a history of previous severe PONV; a history of motion sickness; significant gastrointestinal problems; recent antiemetic drug use; who were older than 60 years or younger than 18 years; who had impaired kidney or liver functions; who were menstruating, pregnant or lactating females; or who were smokers were excluded from the study.
Recruitment/selection of patients	American Society of Anesthesiologists physical status I and II patients of both sexes who were scheduled for elective open cholecystectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin 51.3±16.7; Placebo: 52.1±13.6. Gender (M:F): 7/80. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin 51.3±16.7; Placebo: 52.1±13.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: lower and upper GI (open cholecystectomy).
Indirectness of population	--
Interventions	(n=45) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Patients enrolled in the gabapentin group received 600 mg (two 300 mg tablets). Duration perioperative administration. Concurrent

	medication/care: Pethidine (0.5 mg/kg) was given intravenously to patients who had a pain score more than 4. Patients who had a VAS score more than 4 in nausea also received metoclopramide (10 mg) intravenously.. Indirectness: No indirectness (n=45) Intervention 2: Opioid only. Patients in the placebo group received two placebo (capsules similar in appearance to gabapentin). Duration perioperative administration. Concurrent medication/care: Pethidine (0.5 mg/kg) was given intravenously to patients who had a pain score more than 4. Patients who had a VAS score more than 4 in nausea also received metoclopramide (10 mg) intravenously.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Postoperative pain at postoperatively; Group 1: mean 4.46 pain score (SD 0.83); n=44, Group 2: mean 5.13 pain score (SD 1.24); n=43; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.096
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: drop out; Group 2 Number missing: 2, Reason: drop out

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Pethidine use, milligrams at postoperatively; Group 1: mean 28.33 milligrams (SD 12.9); n=44, Group 2: mean 35.1 milligrams (SD 15.1); n=43; Comments: p value 0.002
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: drop out; Group 2 Number missing: 2, Reason: drop out

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Postoperative nausea at postoperatively; Group 1: 16/44, Group 2: 28/43; Comments: p value 0.021
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: drop out; Group 2 Number missing: 2, Reason: drop out

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Khan 2011[506]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=175)
Countries and setting	Conducted in Iran; Setting: Imam Khomeini medical centre, Tehran.
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I presenting for an elective single level lumbar laminectomy under general anesthesia
Exclusion criteria	Chronic pain syndromes, use of any analgesics or gabapentin 24h before surgery, known allergy to gapapentin, a history of drug or alcohol abuse ora an intake of antacids 48h before operation
Recruitment/selection of patients	scheduled for elective single level lumbar laminectomy under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 43.19 ± 10.69; Placebo: 41.0 ± 10.5. Gender (M:F): 113/62. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 43.19 ± 10.69; Placebo: 41.0 ± 10.5). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 (all patients ASA I). 3. Type of surgery: ortho/large joint replacement (Lumbar Laminectomy).
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Gabapentin (600mg, 900mg or 1200mg) capsules were administered 2 hours before the operation or immediately post incision through a nasogastric tube by a trained nurse. After dissolving the post-incision capsules, the solution was instilled via the nasogastric tube, followed by 15ml of water to expedite its passage into the stomach. . Duration preoperative and intraoperative. Concurrent medication/care: All patients received morphine sulfate based on their demand for pain control. A bolus of 0.07mg/kg morphine sulfate was administered at first demand through a patient controlled analgesia device by the patients themselves. The incremental dose was set at 0.03mg/kg with a lockout interval of 15 minutes. Continuous infusion was not considered. no other analgesic agents were prescribed. . Indirectness: No indirectness (n=25) Intervention 2: Opioid only. Identical placebo capsules were administered 2 hours before the operation or immediately post incision through a nasogastric tube by a trained nurse. After dissolving the post-incision capsules, the solution was instilled via the nasogastric tube, followed by 15ml of water to

Study	Khan 2011[506]
	expedite its passage into the stomach. . Duration preoperative and intraoperative. Concurrent medication/care: All patients received morphine sulfate based on their demand for pain control. A bolus of 0.07mg/kg morphine sulfate was administered at first demand through a patient controlled analgesia device by the patients themselves. The incremental dose was set at 0.03mg/kg with a lockout interval of 15 minutes. Continuous infusion was not considered. no other analgesic agents were prescribed. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score at 0-4 hours at 0-4 hours postoperatively ; Group 1: mean 4.35 pain score (SD 1.413); n=150, Group 2: mean 6.8 pain score (SD 1.1); n=25; visual analgoue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score at 12-24 hours at 12-24 hours postoperatively ; Group 1: mean 2.983 pain score (SD 0.997); n=150, Group 2: mean 3.5 pain score (SD 0.8); n=25; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Total morphine consumption (milligrams) at 24 hours postoperatively ; Group 1: mean 20.8 milligrams (SD 5.776); n=150, Group 2: mean 31.5 milligrams (SD 9.6); n=25; Comments: groups for pre and post incision 600mg, 900mg and 1200mg combined in Gabapentin group
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at postoperatively ; Group 1: 12/150, Group 2: 2/25
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Vomiting at postoperatively ; Group 1: 8/150, Group 2: 1/25
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Khan 2011[506]
- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Drowsiness at postoperatively ; Group 1: 8/150, Group 2: 1/25 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Dizziness at postoperatively ; Group 1: 5/150, Group 2: 1/25 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Khan 2013[505]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=70)
Countries and setting	Conducted in Pakistan; Setting: Anaesthesia Department of Fatima Memorial Hospital, Lahore
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	not specified
Exclusion criteria	not specified
Recruitment/selection of patients	Patients undergoing total abdominal hysterectomy from April, 2007 to January, 2008
Age, gender and ethnicity	Age - Mean (SD): 43.97 ± 4.033. Gender (M:F): not specified. Ethnicity: NA
Further population details	1. Age: <60 years (43.97 ± 4.033). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (total abdominal hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Received oral gabapentin 1200 mg two hours before surgery. Duration preoperatively. Concurrent medication/care: For postoperative analgesia, patients received nalbuphine 0.05 mg/kg IV every two hours by assessing VAS. The first post-operative dose of nalbuphine was given two hours after surgery. In case the pain score was more than 3 (moderate pain) a top up dose of nalbuphine 0.05 mg/kg was administered intravenously and was noted.. Indirectness: No indirectness (n=35) Intervention 2: Opioid only. received oral placebo capsules two hours before surgery. Duration preoperatively. Concurrent medication/care: For postoperative analgesia, patients received nalbuphine 0.05 mg/kg IV every two hours by assessing VAS. The first post-operative dose of nalbuphine was given two hours after surgery. In case the pain score was more than 3 (moderate pain) a top up dose of nalbuphine 0.05 mg/kg was administered intravenously and was noted.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO Protocol outcome 1: Pain (< 6 hours post op) - Actual outcome: Pain score <6 hours at < 6 hours postoperatively; Group 1: mean 3.617 pain score (SD 1.339); n=34, Group 2: mean 5.2 pain score (SD 1.051); n=35; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 0 Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: Pain score at 24 hours at 24 hours postoperatively; Group 1: mean 0.852 pain score (SD 0.743); n=34, Group 2: mean 2.428 pain score (SD 1.118); n=35; visual analogue scale 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Postoperative nalbuphine consumption (in milligrams) at 24 hours postoperatively; Group 1: mean 13.21 (SD 4.708); n=34, Group 2: mean 24.31 (SD 9.276); n=35 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Khurana 2014[508]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in India; Setting: HIHT university, Dehradun, India
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with chronic low back pain persisting up to 6 months in spite of alternative therapies and on radiological intervention diagnosed with intervertebral disc prolapse without ligament hypertrophy posted for lumbar discectomy; minimum VAS at recruitment 4; ASA I or II
Exclusion criteria	history of previous back surgery, history of gastric ulcers or intestinal bleeding, known allergy to the drugs under study, patients with serious medical problems within the last 6 months including myocardial infarction, congestive heart failure, stroke, DVT< pulmonary embolism, kidney disease as evidenced by the need for dialysis, or kidney transplant, patients intending to become pregnant or who are pregnant or nursing during the projected course of treatment and those who were taking gabapentin or pregabalin for other medical purposes.
Recruitment/selection of patients	patients with chronic low back pain persisting up to 6 months in spite of alternative therapies and on radiological intervention diagnosed with intervertebral disc prolapse without ligament hypertrophy posted for lumbar discectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 49 ± 10.4; Pregabalin: 46.9 ± 10.1. Gender (M:F): 46/14. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 49 ± 10.4; Pregabalin: 46.9 ± 10.1). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I: 45; ASA II: 15). 3. Type of surgery: ortho/large joint replacement (Spinal Surgery).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 300mg of Gabapentin 60 minutes preoperatively and 8 hourly for 7 days postoperatively. Duration perioperatively. Concurrent medication/care: 1 to 2 mg/kg Tramadol IV when VAS score >3 (n=30) Intervention 2: Opioid plus neuropathic nerve stabiliser - Pregabalin. 75mg of Pregabalin 60 minutes preoperatively and 8 hourly for 7 days postoperatively. Duration perioperatively. Concurrent medication/care: 1 to 2 mg/kg Tramadol IV when VAS score >3
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PREGABALIN

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Sedation at postoperatively; Group 1: 4/30, Group 2: 3/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Nausea at postoperatively; Group 1: 2/30, Group 2: 4/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0 - Actual outcome: Vomiting at postoperatively; Group 1: 1/30, Group 2: 0/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Kim 2017[518]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA class 1 or 2, scheduled to undergo elective wedge resection or lobectomy underVATSwere enrolled in this randomized, placebo-controlled, double-blind trial.
Exclusion criteria	Patients were excluded in this study if they had severe cardiovascular or respiratory diseases, impaired hepatic and/or renal function, history of chronic use of analgesics and drug abuse, history of dizziness or frequent headache or were morbidly obese patients.
Recruitment/selection of patients	FromDecember 2012 to April 2014, 60 adult patients (aged 20–65 years),ASAclass 1 or 2, scheduled to undergo elective wedge resection or lobectomy under VATS
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 56±12; Placebo: 58±9. Gender (M:F): 30/30. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 56±12; Placebo: 58±9). 2. American Society of Anesthesiologists (ASA)

	Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: Not stated / Unclear (video-assisted thorascopic surgery).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. The pregabalin group received oral pregabalin 150mg orally 1hour before the anesthetic induction. Duration intraoperatively. Concurrent medication/care: After completion of the surgical procedure, IV-PCA. The IV-PCA regimen consisted of fentanyl 20mgkg□1 in 0.9% saline (total volume; 100mL) was programmed to deliver 1mL each time the patient pressed the activation button, with a 15minutes lockout interval, no fentanyl bolus before initiation. If the patient requested additional analgesic or the patient's NRS score was ≥5, tramadol 0.7mgkg was administered intravenously and repeated if required.. Indirectness: No indirectness (n=30) Intervention 2: Opioid only. The placebo group received placebo drug orally 1hour before the anesthetic induction.. Duration intraoperatively. Concurrent medication/care: After completion of the surgical procedure, IV-PCA. The IV-PCA regimen consisted of fentanyl 20mgkg□1 in 0.9% saline (total volume; 100mL) was programmed to deliver 1mL each time the patient pressed the activation button, with a 15minutes lockout interval, no fentanyl bolus before initiation. If the patient requested additional analgesic or the patient's NRS score was ≥5, tramadol 0.7mgkg was administered intravenously and repeated if required.. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score < 6 hours at 6 hours postoperatively; Group 1: mean 3.8 (SD 1.9); n=30, Group 2: mean 5.6 (SD 1.4); n=30; visual analogue scale 0-10 Top=High is poor outcome; Comments: P value 0.001
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: pain score 24 hours at 24 hours postoperatively; Group 1: mean 2.6 pain score (SD 1.6); n=30, Group 2: mean 3.5 pain score (SD 1.5); n=30; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.029
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: PCA Nalbuphine volume accumulated, mL at 6 hours postoperatively; Group 1: mean 17 millilitres (SD 3); n=30, Group 2: mean 20 millilitres (SD 4); n=30; Comments: p value 0.715
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

	- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: PCA Nalbuphine volume accumulated, mL at 24 hours postoperatively; Group 1: mean 40 millilitres (SD 5); n=30, Group 2: mean 44 millilitres (SD 4); n=30; Comments: p value 0.257 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Sedation 6 hours at 6 hours postoperatively; Group 1: 1/30, Group 2: 0/30; Comments: p value 0.313 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Sedation 24 hours at 24 hours postoperatively; Group 1: 0/30, Group 2: 0/30; Comments: p value 1 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Headache 6 hours at 6 hours postoperatively; Group 1: 5/30, Group 2: 4/30; Comments: p value 0.718 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Headache 24 hours at 24 hours postoperatively; Group 1: 3/30, Group 2: 4/30; Comments: p value 0.688 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Dizziness 6 hours at 6 hours postoperatively; Group 1: 2/30, Group 2: 2/30; Comments: p value 1 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Dizziness 24 hours at 24 hours postoperatively; Group 1: 1/30, Group 2: 3/30; Comments: p value 0.301 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Nausea 6 hours at 6 hours postoperatively; Group 1: 7/30, Group 2: 7/30; Comments: p value 0.856 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Nausea 24 hours at 24 hours postoperatively; Group 1: 3/30, Group 2: 5/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Leung 2006[601]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=21)
Countries and setting	Conducted in Denmark, USA; Setting: University of California, San Francisco Medical centre, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients who were ≥45 years, undergoing surgery involving the spine, requiring general anesthesia and expected to remain in the hospital postoperatively for ≥72 hours
Exclusion criteria	patients who could not complete the delirium testing, already taking preoperative gabapentin or with sensitivity to gabapentin
Recruitment/selection of patients	consecutive patients undergoing spinal surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 57.2 ± 10.3; Placebo: 61.4 ± 11.3. Gender (M:F): 11/10. Ethnicity: NA
Further population details	1. Age: >60 years (Gabapentin: 57.2 ± 10.3; Placebo: 61.4 ± 11.3). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I - II: 11; ASA III - IV: 10). 3. Type of surgery: ortho/large joint replacement (Spinal surgery).
Indirectness of population	--
Interventions	(n=9) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Gabapentin 900mg administered 1 to 2 hours before surgery and anesthesia. This dose was continued for the first 3 postoperative days. . Duration preoperatively up to 3 days postoperatively . Concurrent medication/care: PCA IV hydromorphone (n=12) Intervention 2: Opioid only. Placebo administered 1 to 2 hours before surgery and anesthesia. This dose was continued for the first 3 postoperative days. . Duration preoperatively up to 3 days postoperatively . Concurrent medication/care: PCA IV hydromorphone. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO	

Protocol outcome 1: Pain (>6-24 hours post op)
- Actual outcome: Average pain score at 24 hours postoperatively; Group 1: mean 6.3 pain score (SD 1.8); n=9, Group 2: mean 5.4 pain score (SD 2.1); n=12; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Postoperative use of Hydromorphone PCA at 24 hours postoperatively; Group 1: mean 2.78 milligrams (SD 2.26); n=9, Group 2: mean 13.54 milligrams (SD 25.31); n=12
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Marashi 2012[668]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=66)
Countries and setting	Conducted in Iran; Setting: Tehran University of Medical Sciences, Tehran, Iran
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I and II whom underwent total thyroidectomy without lymph node dissection (Patients studied were previously diagnosed with multi- nodular goiter)
Exclusion criteria	history of cardiovascular, hepatic or renal disease, chronic pain, hypertension, motion sickness, history of

	any kinds of allergy to clonidine, gabapentin or common drugs that are used during general anesthesia, history of drug or alcohol abuse and taking gabapentin regimen before the surgery except for the study protocol.
Recruitment/selection of patients	underwent total thyroidectomy without lymph node dissection
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 38.5 ± 10.1; Placebo: 38.2 ± 10.0. Gender (M:F): 33/11. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 38.5 ± 10.1; Placebo: 38.2 ± 10.0). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 24; ASA II: 20). 3. Type of surgery: Not applicable (Thyroidectomy).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. patients received three capsules, each containing 300 mg (a total of 900 mg) gabapentin, two hours before surgery. Duration preoperatively . Concurrent medication/care: In the cases of postoperative pain with the VAS score over of four, 0.1 mg/kg morphine was administered for the patients. If more analgesic was required, the interval between two injections was at least four hours.. Indirectness: No indirectness (n=22) Intervention 2: Opioid only. Placebo capsules given 2 hours before surgery. Duration preoperatively . Concurrent medication/care: In the cases of postoperative pain with the VAS score over of four, 0.1 mg/kg morphine was administered for the patients. If more analgesic was required, the interval between two injections was at least four hours.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score 6 hours postoperatively at < 6 hours postoperatively; Group 1: mean 3.6 pain score (SD 0.7); n=22, Group 2: mean 5.9 pain score (SD 0.9); n=22; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain score 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 3.5 pain score (SD 0.7); n=22, Group 2: mean 3.5 pain score (SD 0.7); n=22; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine consumption at 24 hours postoperatively; Group 1: mean 18.3 milligrams (SD 15.6); n=22, Group 2: mean 65.7 milligrams

(SD 31.1); n=22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Mardani-Kivi 2013[671]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=114)
Countries and setting	Conducted in Iran; Setting: Guilan University of Medical Sciences, Rasht, Iran
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	age between 18-55 years, physical condition type I or II in ASA (American Society of Anesthesiology), operation duration time less than one hour, and no concurrent lesions identified during arthroscopy.
Exclusion criteria	associated tearing of other ligaments and or meniscii, presence of any chondral lesions, a known allergy to gabapentin, psychological disorders, alcohol or drug abuse, and regular consumption of analgesics, corticosteroids or anticonvulsants.
Recruitment/selection of patients	patients whom were candidate for arthroscopic ACL reconstruction
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 32.2±9.3; Placebo: 30.5±10.2. Gender (M:F): 100/14. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 32.2±9.3; Placebo: 30.5±10.2). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (I or II in ASA). 3. Type of surgery: ortho/large joint replacement (Anterior Cruciate Ligament Reconstruction).

Indirectness of population	--
Interventions	(n=57) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 600mg of gabapentin. Duration 2 hours preoperatively. Concurrent medication/care: On-demand pethedine (0.5mg/Kg) was injected for patients' pain management in the first 24 h post-operation. No other sedatives or analgesics were given to the patients during the follow-up period.. Indirectness: No indirectness (n=57) Intervention 2: Opioid only. Patients given identical-looking placebo. The placebo was provided in identical form to the origi- nal capsule by the same pharmaceutical company.. Duration 2 hours preoperatively. Concurrent medication/care: On-demand pethedine (0.5mg/Kg) was injected for patients' pain management in the first 24 h post-operation. No other sedatives or analgesics were given to the patients during the follow-up period.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain < 6 hours postoperatively at 6 hours postoperatively; Group 1: mean 4.8 pain score (SD 2.08); n=55, Group 2: mean 6.9 pain score (SD 1.86); n=53; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Pethidine Consumption < 6 hours postoperatively at 6 hours postoperatively; Group 1: mean 20 milligrams (SD 23.84); n=55, Group 2: mean 34 milligrams (SD 21); n=53
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives
- Actual outcome: Pethidine Consumption 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 25 milligrams (SD 23.84); n=55, Group 2: mean 37 milligrams (SD 25.26); n=53
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic

side effects) - Actual outcome: Nausea and vomiting < 6 hours postoperatively at 6 hours postoperatively; Group 1: 5/55, Group 2: 7/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives - Actual outcome: Nausea and vomiting 24 hours postoperatively at 24 hours postoperatively; Group 1: 3/55, Group 2: 4/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives - Actual outcome: Dizziness < 6 hours postoperatively at 6 hours postoperatively; Group 1: 7/55, Group 2: 4/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives - Actual outcome: Dizziness 24 hours postoperatively at 24 hours postoperatively; Group 1: 3/55, Group 2: 6/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives - Actual outcome: Sedation < 6 hours postoperatively at 6 hours postoperatively; Group 1: 6/55, Group 2: 3/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives - Actual outcome: Sedation 24 hours postoperatively at 24 hours postoperatively; Group 1: 2/55, Group 2: 3/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: received other sedatives; Group 2 Number missing: 4, Reason: received other sedatives	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Mardani-Kivi 2016[670]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=76)
Countries and setting	Conducted in Iran; Setting: Tertiary Centre, Iran

Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	aged between 18–75, types I or II in ASA physical status, operation duration time less than one hour and no concomitant lesions diagnosed during arthroscopy.
Exclusion criteria	The exclusion criteria were the presence of any accompanied cartilage lesions, any known allergy to gabapentin, having previous history of epilepsy, hepatic, renal or psychological disorders, alcohol and/or drug abuse and daily consumption of analgesics, corticoesteriods or anticonvulsants
Recruitment/selection of patients	patients diagnosed with shoulder bankart lesion, candidates for arthroscopic surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 30.2 ± 5; Placebo: 28.3 ± 4.4. Gender (M:F): 57/19. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 30.2 ± 5; Placebo: 28.3 ± 4.4). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: ortho/large joint replacement (arthroscopic shoulder surgery).
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. gabapentin 600 mg two hours prior to the operation. Duration preoperatively . Concurrent medication/care: pethedine (0.5 mg/kg) was injected on demand. None of the patients received other opioids or analgesics perioperatively. Indirectness: No indirectness (n=38) Intervention 2: Opioid only. identical placebo administered two hours before the operation. The placebo capsules were produced in the form identical to the active counterparts manufactured by the same company.. Duration preoperatively. Concurrent medication/care: pethedine (0.5 mg/kg) was injected on demand. None of the patients received other opioids or analgesics perioperatively. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)

- Actual outcome: pain score < 6 hours at 6 hours postoperatively; Group 1: mean 4.9 pain score (SD 1.09); n=37, Group 2: mean 5.4 pain score (SD 1.04); n=34; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: pain score at 24 hours at 24 hours postoperatively; Group 1: mean 4.7 pain score (SD 1.4); n=37, Group 2: mean 5.3 pain score (SD 1.04); n=34; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Pethidine Consumption 6 hours at 6 hours postoperatively; Group 1: mean 20.5 milligrams (SD 13.34); n=37, Group 2: mean 40.3 milligrams (SD 9.82); n=34; Comments: p value < 0.0001
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal

Protocol outcome 4: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Pethidine Consumption at 24 hours at 24 hours postoperatively; Group 1: mean 18.4 milligrams (SD 15.52); n=37, Group 2: mean 40 milligrams (SD 24.09); n=34; Comments: p value <0.0001
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal

Protocol outcome 5: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: dizziness < 6 hours at 6 hours postoperatively; Group 1: 6/37, Group 2: 8/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal
- Actual outcome: Dizziness 24 hours at 24 hours postoperatively; Group 1: 5/37, Group 2: 3/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal
- Actual outcome: Sedation < 6 hours at 6 hours postoperatively; Group 1: 5/37, Group 2: 4/34

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal - Actual outcome: Sedation 24 hours at 24 hours postoperatively; Group 1: 3/37, Group 2: 2/34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal - Actual outcome: Nausea and vomiting < 6 hours at 6 hours postoperatively; Group 1: 1/37, Group 2: 11/34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal - Actual outcome: Nausea and vomiting 24 hours at 24 hours postoperatively; Group 1: 1/37, Group 2: 2/34 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: took other analgesia; Group 2 Number missing: 4, Reason: took other analgesia; withdrawal	
Protocol outcomes not reported by the study	Quality of life ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Metry 2008[714]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=111)
Countries and setting	Conducted in Egypt; Setting: Ain Shams University, Cairo, Egypt
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18-75, scheduled for unilateral modified radical mastectomy with auxillary dissection
Exclusion criteria	unable to cooperate, had known allergy to gabapentin or morphine, a history of drug or alcohol abuse, chronic pain or daily intake of analgesics or corticosteroids, diabetes, or impaired kidney function. Patients

	with NSAIDs or paracetamol intake 24h prior to operation of an intake of antacids 48h prior to operation were also excluded from the study.
Recruitment/selection of patients	scheduled for unilateral modified radical mastectomy with auxillary dissection
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 57.45 ± 7.806; Placebo: 58.6 ± 8.9. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 57.45 ± 7.806; Placebo: 58.6 ± 8.9). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: Not applicable (modified randical mastectomy with auxillary dissection).
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. two hours prior to induction of anesthesia or two hours after the end of surgery patients received 1200mg of Gabapentin. Duration preoperatively and postoperatively. Concurrent medication/care: all patients received morphine 3mg IV every 10 minutes until VAS scores were 4 or less at rest and 6 or less during mobilization.. Indirectness: No indirectness (n=37) Intervention 2: Opioid only. two hours prior to induction of anesthesia or two hours after the end of surgery patients received Placebo . Duration preoperatively and postoperative. Concurrent medication/care: all patients received morphine 3mg IV every 10 minutes until VAS scores were 4 or less at rest and 6 or less during mobilization.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain scores at 6 hours at 6 hours postoperatively; Group 1: mean 1.252 pain score (SD 0.956); n=67, Group 2: mean 2.41 pain score (SD 1.3); n=34; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 3

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain scores at 24 hours at 24 hours postoperatively; Group 1: mean 1.849 pain score (SD 1.506); n=67, Group 2: mean 2.3 pain score (SD 1.3); n=34; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 3

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)

- Actual outcome: Total morphine consumption at 24 hours postoperatively; Group 1: mean 16.09 milligrams (SD 7.788); n=67, Group 2: mean 29.2 milligrams (SD 9.6); n=34 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 3 Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Vomiting at postoperatively; Group 1: 2/67, Group 2: 1/34 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Mishra 2016[724]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in India; Setting: S. R. N. Hospital of M. L. N. Medical College, Allahabad, India
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	American Society of Anesthesiologists status I and II of either sex in the age group of 20–60 years, weighing 40–70 kg, scheduled for elective laparoscopic cholecystectomy
Exclusion criteria	known history of hypersensitivity to drugs to be used, history of drug or alcohol abuse, uncontrolled concomitant medical diseases (hypertension, bronchial asthma, diabetes mellitus), patients with history of chronic pain conditions, impaired kidney or liver function, daily intake of analgesics or corticosteroids and intake of nonsteroidal anti-inflammatory drugs or paracetamol 24 h before operation, laparoscopic cholecystectomy converted into open cholecystectomy, and patients on anticoagulant therapy or antidepressants and obesity
Recruitment/selection of patients	scheduled for elective laparoscopic cholecystectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 37 ± 9.37; Pregabalin: 35.8 ± 8.43. Gender (M:F): 26/34. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 37 ± 9.37; Pregabalin: 35.8 ± 8.43). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: lower and upper GI (laparoscopic cholecystectomy).
Extra comments	.
Indirectness of population	--
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Gabapentin - 30 patients who received 900 mg oral gabapentin in the form of 3 capsules containing 300 mg of gabapentin about 1 h prior to the induction of anesthesia. Duration preoperatively. Concurrent medication/care: Whenever the pain score of a particular patient was ≥4, the patient was given injection tramadol (1 mg/kg) i.v. as a rescue analgesic.. Indirectness: No indirectness (n=30) Intervention 2: Opioid plus neuropathic nerve stabiliser - Pregabalin. Pregabalin - 30 patients who received 150 mg oral pregabalin in the form of 2 capsules containing 75 mg pregabalin about 1 h prior to the

	induction of anesthesia.. Duration preoperatively. Concurrent medication/care: Whenever the pain score of a particular patient was ≥4, the patient was given injection tramadol (1 mg/kg) i.v. as a rescue analgesic.. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PREGABALIN

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain <6 hours postoperatively at 6 hours postoperatively; Group 1: mean 3.07 pain score (SD 0.44); n=30, Group 2: mean 4.48 pain score (SD 0.26); n=30; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: pain 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 2.01 pain score (SD 0.34); n=30, Group 2: mean 1.97 pain score (SD 0.25); n=30; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Total Tramadol used at 24 hours postoperatively; Group 1: mean 116.13 milligrams (SD 14.08); n=30, Group 2: mean 64.67 milligrams (SD 16.69); n=30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Sedation at 24 hours postoperatively; Group 1: 12/30, Group 2: 14/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Nausea at 24 hours postoperatively; Group 1: 5/30, Group 2: 4/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Respiratory Depression at ≤24 hours postoperatively; Group 1: 2/30, Group 2: 3/30
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ;

study	Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Mohammadi 2008[737]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=70)
Countries and setting	Conducted in Iran; Setting: Dr Shariati Hospital or Tehran University of Medical Sciences.
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II, aged 20 - 45, scheduled for outpatient laparoscopic surgery under general anesthesia.
Exclusion criteria	known allergy to study medications and those receiving psychotropic drugs
Recruitment/selection of patients	scheduled for outpatient laparoscopic surgery under general anesthesia, August to December 2007
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 31.3 ± 5.4; Placebo: 31.9 ± 5.6. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 31.3 ± 5.4; Placebo: 31.9 ± 5.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: gynae-oncology (laparoscopic surgery for assisted reproductive technologies).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Patients within this group received 400mg Gabapentin 1 hour before surgery. Duration preoperative administration. Concurrent medication/care: fentanyl was used as rescue postoperative analgesic and Ondansetron 4mg IV as rescue medication for emesis (n=35) Intervention 2: Opioid only. Placebo tablet given 1 hour before surgery. Duration preoperative administration. Concurrent medication/care: fentanyl was used as rescue postoperative analgesic and Ondansetron 4mg IV as rescue medication for emesis. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score < 6 hours postoperatively at < 6 hours postoperatively; Median VAS score (IQR): Gabapentin: 3 (2 - 3); Placebo: 3 (3 - 5) pain score Visual Analogue scale 0-10 Top=High is poor outcome, Comments: p value 0.002;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at postoperatively; Group 1: 2/35, Group 2: 9/35; Comments: p value 0.022
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Vomiting at postoperatively; Group 1: 0/35, Group 2: 4/35; Comments: p value 0.114
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Mohammed 2012[738]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in Egypt; Setting: Department of Anesthesia, Faculty of Medicine, Ain Shams University, Egypt
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I–II patients, scheduled to undergo elective functional endoscopic sinus surgery. Patients were chosen

	to participate in the study if they were at least 18 years old, willing to comply with the postoperative follow-up evaluations, within 50% of ideal body weight, had no clinically significant cardiovascular or central nervous system disease, and could operate a patient-controlled analgesia (PCA) device
Exclusion criteria	18 years or older than 50 years, history of chronic pain, regular medications with analgesics, analgesic use within 24 h of surgery, drug or alcohol abuse, psychiatric disorders, known allergy or contra-indications to anesthetics or any drug used, asthma, renal insufficiency, hepatic disorder, history of a peptic ulcer or bleeding diathesis and pregnancy
Recruitment/selection of patients	scheduled to undergo elective functional endoscopic sinus surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 30.6±6.1; Placebo: 33.7±4.2. Gender (M:F): not specified. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 30.6±6.1; Placebo: 33.7±4.2). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I: 71; ASA II: 9). 3. Type of surgery: Not applicable (elective functional endoscopic sinus surgery).
Indirectness of population	--
Interventions	(n=40) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. patients received oral gabapentin 1.2 g 1 h before scheduled time for surgery. Duration preoperatively. Concurrent medication/care: After arrival in the post anesthesia care unit (PACU), patients were connected to a PCA device and postoperative analgesia was provided using 2 mg IV bolus injections of morphine at a lockout interval of 10 min and with a maximum 4 h limit of 40 mg. The incremental bolus dose of morphine was increased to 3 mg if analgesia was inadequate (pain score by visual analogue scale (VAS) was more than 4 cm after the first hour of PCA use. . Indirectness: No indirectness (n=40) Intervention 2: Opioid only. received oral placebo capsules before scheduled time for surgery. Duration preoperatively. Concurrent medication/care: After arrival in the post anesthesia care unit (PACU), patients were connected to a PCA device and postoperative analgesia was provided using 2 mg IV bolus injections of morphine at a lockout interval of 10 min and with a maximum 4 h limit of 40 mg. The incremental bolus dose of morphine was increased to 3 mg if analgesia was inadequate (pain score by visual analogue scale (VAS) was more than 4 cm after the first hour of PCA use. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)

- Actual outcome: Morphine Consumption at 6 - 24 hours postoperatively; Group 1: mean 8 milligrams (SD 1); n=40, Group 2: mean 14 milligrams (SD 2); n=40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Nausea at postoperatively; Group 1: 3/40, Group 2: 10/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 1/40, Group 2: 5/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Urinary Retention at postoperatively; Group 1: 0/40, Group 2: 1/40 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Montazeri 2007[745]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=70)
Countries and setting	Conducted in Iran; Setting: Department of Anaesthesiology and Intensive Care Medicine, Isfahan University, Isfahan, Iran
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) age 16-70 years; (2) ASA physiological status I -II; (3) duration of surgery between 1.5-2 hours; and (4) scheduled for knee arthroscopy
Exclusion criteria	(1) known allergy against gabapentin; (2) epilepsy; (3) previous treatment with gabapentin; (4) chronic pain syndrome; (5) psychiatric disorder; (6) substance abuse; (7) impaired kidney or liver function; and (8) patients who had received analgesics within 48 hours before surgery
Recruitment/selection of patients	scheduled for knee arthroscopy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 34.7 ± 18.1; Placebo: 34.6 ± 17.8. Gender (M:F): 54/16. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 34.7 ± 18.1; Placebo: 34.6 ± 17.8). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: ortho/large joint replacement (knee arthroscopy).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 300 mg capsule of gabapentin was given to the patients about two hours before induction of anaesthesia.. Duration preoperatively. Concurrent medication/care: Patients received morphine 0.05 mg/kg IV on demand.. Indirectness: No indirectness (n=35) Intervention 2: Opioid only. One placebo capsule was given to the patients within this group. The size and shape of the capsules for both groups looked similar. The medication was given to the patients about two hours before induction of anaesthesia.. Duration preoperatively. Concurrent medication/care: Patients received morphine 0.05 mg/kg IV on demand.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain < 6 hours postoperatively at < 6 hours postoperatively; Group 1: mean 5.73 pain score (SD 1.93); n=35, Group 2: mean 7.05 pain score (SD 1.81); n=35; Visual Analogue Scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 4.46 pain score (SD 1.764); n=35, Group 2: mean 6.65 pain score (SD 2.57); n=35; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Total 24 hour morphine consumption (milligrams) at 24 hours postoperatively; Group 1: mean 15.43 milligrams (SD 2.54); n=35, Group 2: mean 17.94 milligrams (SD 3); n=35
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at Postoperatively; Group 1: 6/35, Group 2: 5/35
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Vomiting at Postoperatively; Group 1: 4/35, Group 2: 3/35
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Dizziness at Postoperatively; Group 1: 1/35, Group 2: 0/35
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Nesioonpour 2014[906]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=62)
Countries and setting	Conducted in Iran; Setting: Imam Khomeini Hospital, Iran
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>18 years of age, weighing at least 40kg and ASA I
Exclusion criteria	History of opioid hypersensitivity, renal failure, anticipated difficult intubation, comorbidities, and ASA III - IV
Recruitment/selection of patients	candidates for nasal septoplasty surgery following the diagnosis of nasal septum deviation made by an ENT specialist
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 28.43 ± 10.43; Placebo: 28.81 ± 10.44. Gender (M:F): 35/27. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 28.43 ± 10.43; Placebo: 28.81 ± 10.44). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 (all patients ASA I). 3. Type of surgery: Not applicable (Nasal Septoplasty).
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 800mg oral gabapentin as two 400mg capsules one hour before surgery. Duration preoperative. Concurrent medication/care: IV pethidine 0.3mg/kg was considered to be administered in case of VAS at or above 3. Indirectness: No indirectness (n=31) Intervention 2: Opioid only. two placebo capsules one hour before surgery. Duration preoperative. Concurrent medication/care: IV pethidine 0.3mg/kg was considered to be administered in case of VAS at or above 3. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score 4 hours at < 6 hours postoperatively; Group 1: mean 2.26 pain score (SD 1.23); n=31, Group 2: mean 3.77 pain score (SD

1.68); n=31; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.012 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Pain (>6-24 hours post op) - Actual outcome: pain score 24 hours at 24 hours postoperatively; Group 1: mean 4.68 pain score (SD 2.02); n=31, Group 2: mean 6.58 pain score (SD 2.51); n=31; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.101 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Total pethidine consumption at 24 hours postoperatively; Group 1: mean 13.54 milligrams (SD 14.67); n=31, Group 2: mean 53.22 milligrams (SD 17.67); n=31; Comments: p value 0.049 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Ozgencil 2011[951]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Turkey; Setting: Department of Anaesthesiology and Reanimation, Medical Faculty of Ankara University, Turkey
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients who were scheduled to undergo elective decompressive

	lumbar laminectomy and discectomy.
Exclusion criteria	age < 18 years; age > 70 years; pregnant; allergic and/ or contraindicated to one or more of the drugs studied; ASA score III and above; having drug and/or alcohol addiction, renal failure, diabetes mellitus or epilepsy; and currently using opioids for chronic pain and/or any of the drugs studied.
Recruitment/selection of patients	patients who were scheduled to undergo elective decompressive lumbar laminectomy and discectomy.
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 50.6 ± 9.1; Pregabalin: 51.9 ± 7.1. Gender (M:F): 28/32. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 50.6 ± 9.1; Pregabalin: 51.9 ± 7.1). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: ortho/large joint replacement (decompressive lumbar laminectomy and discectomy).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Patients received gabapentin 600 mg at two hours prior to the operation, and ten and 22 hours after the operation (over two days).. Duration preoperatilvely up to 48 hours postoperatively. Concurrent medication/care: PCA pump was set to deliver a loading dose of 2.5 mg and an incremental dose of 2.5 mg at a lockout interval of eight minutes and a four-hour limit of 50 mg. The incremental dose was increased to 3 mg, the lock -out interval decreased to six minutes and the four hour limit increased to 60 mg, whenever the analgesia was inadequate after one hour. (n=30) Intervention 2: Opioid plus neuropathic nerve stabiliser - Pregabalin. Patients received Pregabalin 150mg at two hours prior to the operation, and ten and 22 hours after the operation (over two days).. Duration preoperatively up to 48 hours postoperatively. Concurrent medication/care: PCA pump was set to deliver a loading dose of 2.5 mg and an incremental dose of 2.5 mg at a lockout interval of eight minutes and a four-hour limit of 50 mg. The incremental dose was increased to 3 mg, the lock -out interval decreased to six minutes and the four hour limit increased to 60 mg, whenever the analgesia was inadequate after one hour.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PREGABALIN

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score 6 hours postoperatively at <6 hours postoperatively; Group 1: mean 2.4 pain score (SD 0.67); n=30, Group 2: mean 2.36

pain score (SD 0.92); n=30; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: pain score 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 1.1 pain score (SD 0.48); n=30, Group 2: mean 1.1 pain score (SD 1.18); n=30; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine consumption at 24 hours postoperatively; Group 1: mean 29.47 Milligrams (SD 9.64); n=30, Group 2: mean 36.33 Milligrams (SD 9.41); n=30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at 24 hours postoperatively; Group 1: 8/30, Group 2: 5/30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Vomiting at 24 hours postoperatively; Group 1: 3/30, Group 2: 3/30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Dizziness at 24 hours postoperatively; Group 1: 9/30, Group 2: 8/30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Somnolance at 24 hours postoperatively; Group 1: 8/30, Group 2: 7/30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0
- Actual outcome: Headache at 24 hours postoperatively; Group 1: 5/30, Group 2: 2/30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Urine Retention at 24 hours postoperatively; Group 1: 4/30, Group 2: 5/30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Pruritus at 24 hours postoperatively; Group 1: 5/30, Group 2: 4/30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Pandey 2004[964]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=459)
Countries and setting	Conducted in India
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA physical status I and II of both sexes scheduled for elective laparoscopic cholecystectomy
Exclusion criteria	body weight exceeding 20% of the ideal body weight; age older than 70 yr or younger than 18 yr; known history of hypersensitivity to any drug; history of drug or alcohol abuse; uncontrolled concomitant medical dis- eases (hypertension, bronchial asthma, diabetes mellitus); patients with history of chronic pain conditions; impaired kidney or liver function; cholelithiasis with known common bile duct pathology or indications of cholecystectomy other than cholelithiasis, laparoscopic cholecystectomy converted into open cholecystectomy; and the administration of analgesics within 48 hr of scheduled surgery.
Recruitment/selection of patients	scheduled for elective laparoscopic cholecystectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 41.65 ± 11.19; Tramadol: 40.03 ± 10.84. Gender (M:F): 99/207. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 41.65 ± 11.19; Tramadol: 40.03 ± 10.84). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: lower and upper GI (laparoscopic cholecystectomy).
Indirectness of population	Serious indirectness: Gabapentin versus Opioid, not in addition to Opioid
Interventions	(n=153) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. oral 300 mg gabapentin, two hours before surgery. Duration preoperatively. Concurrent medication/care: 2 μg·kg–1 fentanyl was administered intravenously by a staff nurse as a rescue analgesic at the patient's demand. Indirectness:

	Serious indirectness; Indirectness comment: Gabapentin versus Opioid, not in addition to Opioid (n=153) Intervention 2: Opioid only. 100 mg tramadol or a matching placebo two hours before surgery. Duration preoperatively. Concurrent medication/care: 2 µg·kg–1 fentanyl was administered intravenously by a staff nurse as a rescue analgesic at the patient's demand. Indirectness: Serious indirectness; Indirectness comment: Gabapentin versus Opioid, not in addition to Opioid
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus TRAMADOL

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score <6 hours postoperatively at <6 hours postoperatively; Group 1: mean 2.65 pain score (SD 3); n=153, Group 2: mean 2.97 pain score (SD 2.35); n=153; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 0.65 pain score (SD 0.61); n=153, Group 2: mean 0.87 pain score (SD 0.61); n=153; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Total Fentanyl consumption (micrograms) at 24 hours postoperatively; Group 1: mean 221.16 micrograms (µg) (SD 52.39); n=153, Group 2: mean 269.6 micrograms (µg) (SD 44.17); n=153
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Sedation at 24 hours postoperatively; Group 1: 52/153, Group 2: 44/153
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Nausea & Vomiting at 24 hours postoperatively; Group 1: 38/153, Group 2: 26/153
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Respiratory depression at 24 hours postoperatively; Group 1: 0/153, Group 2: 6/153

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Pandey 2004[965]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=56)
Countries and setting	Conducted in India; Setting: Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I and II, of both sexes scheduled for single-level lumbar disc surgery
Exclusion criteria	body weight exceeding 20% of the ideal body weight; those older than 70 yr or younger than 18 yr; history of drug or alcohol abuse; impaired kidney or liver functions; patients with spondylolisthesis undergoing spinal plating or those with additional pathology of the spine; and patients who had received analgesics within 48 hr before surgery
Recruitment/selection of patients	scheduled for single-level lumbar disc surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 38.5 ± 7.7; Placebo: 39.1 ± 11.6. Gender (M:F): 38/18. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 38.5 ± 7.7; Placebo: 39.1 ± 11.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: ortho/large joint replacement (single-level lumbar disc surgery).
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. oral gabapentin 300 mg two hours before surgery.. Duration preoperatively. Concurrent medication/care: Patients received fentanyl 2 (micrograms) µg·kg–1 on demand. Indirectness: No indirectness

	(n=28) Intervention 2: Opioid only. matching placebo two hours before surgery.. Duration preoperatively. Concurrent medication/care: Patients received fentanyl 2 (micrograms) µg·kg–1 on demand. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score 0-6 hours at <6 hours postoperatively; Group 1: mean 3.5 pain score (SD 2.3); n=28, Group 2: mean 6.1 pain score (SD 1.7); n=28; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value <0.05
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 12-24 hours at ≤24 hours postoperatively; Group 1: mean 1.2 pain score (SD 1.3); n=28, Group 2: mean 2.1 pain score (SD 1.2); n=28; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value < 0.05
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Fentanyl Consumption at 24 hours postoperatively; Group 1: mean 233.5 Micrograms (SD 141.9); n=28, Group 2: mean 359.6 Micrograms (SD 104.1); n=28
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at postoperatively; Group 1: 5/28, Group 2: 4/28
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Vomiting at postoperatively; Group 1: 3/28, Group 2: 4/28
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Dizziness at postoperatively; Group 1: 1/28, Group 2: 0/28
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: light headed at postoperatively; Group 1: 1/28, Group 2: 0/28

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Pandey 2005[962]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in India
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I and II, scheduled for single level lumbar disk surgery
Exclusion criteria	body weight >20% of the ideal body weight, age >70 years or <18 years, history of hypersensitivity to any drug, history of peptic ulcer disease or of bleeding diathesis or taking antacids, uncontrolled concomitant medical diseases (diabetes, hypertension), acute exacerbation of bronchial asthma , impaired kidney or liver function, spondylolisthesis to be treated with spinal plating or additional pathology of the spine, ingestion of analgesics within 24 hours before scheduled surgery or sedatives other than those determined by protocol, history of amenorrhea in patients of reproductive age or pregnancy, antidepressant and calcium channel blocker use, and inadequate skill in using PCA pump.
Recruitment/selection of patients	scheduled for single level lumbar disk surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 41.6± 12.03; Placebo: 36.9±11.5. Gender (M:F): 67/33. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 41.6± 12.03; Placebo: 36.9±11.5). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: ortho/large joint replacement (single level lumbar disk surgery).
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 2 hours before surgery patients

	received Gabapentin and additional placebo capsules (300mg Gabapentin + 4 placebo capsules; 600mg Gabapentin + 3 placebo capsules; 900mg Gabapentin + 2 placebo capsules; 1200mg Gabapentin + 1 placebo capsule). Duration preoperative. Concurrent medication/care: Fentanyl 1.0 µg/kg on each demand with a lockout of 10 minutes (n=20) Intervention 2: Opioid only. 5 capsules of placebo matching gabapentin . Duration preoperative. Concurrent medication/care: Fentanyl 1.0 µg/kg on each demand with a lockout of 10 minutes. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score at 6 hours at 6 hours postoperatively; Group 1: mean 3.65 pain score (SD 1.314); n=80, Group 2: mean 6.15 pain score (SD 1.3); n=20; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score at 24 hours at 24 hours postoperatively; Group 1: mean 2.575 pain score (SD 1.53); n=80, Group 2: mean 4.5 pain score (SD 1.4); n=20; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Fentanyl consumption at 24 hours at 24 hours postoperatively; Group 1: mean 737.9 Micrograms (SD 205.3); n=80, Group 2: mean 1217.5 Micrograms (SD 182); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Respiratory despression at postoperatively; Group 1: 7/80, Group 2: 1/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Nausea at postoperatively; Group 1: 5/80, Group 2: 1/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: -- ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 7/80, Group 2: 2/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: --; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Lightheaded at postoperatively; Group 1: 4/80, Group 2: 2/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Pandey 2005[966]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in India; Setting: Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	ASA I, healthy kidney donors of both sexes and scheduled for open donor nephrectomy
Exclusion criteria	those who exceeded 20% of ideal body weight; were older than 60 yr or younger than 18 yr; had a history of hypersensitivity to any drug, or had a history of peptic ulcer. Excluded also were subjects who had received analgesics within 24 hr before scheduled surgery or received sedatives other than those determined by protocol, subjects on antidepressant and calcium channels blockers, or those who could not demonstrate adequate skill to use patient-controlled-analgesia (PCA) pump.
Recruitment/selection of patients	scheduled for open donor nephrectomy.
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 44.6 ± 10.47; Placebo: 41.5 ± 12.3. Gender (M:F): 19/41. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 44.6 ± 10.47; Placebo: 41.5 ± 12.3). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 3. Type of surgery: Not stated / Unclear (open donor

	nephrectomy).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. received two capsules of gabapentin 300 mg each two hours before surgery or two capsules of gabapentin 300 mg each through a nasogastric tube after surgical incision. Duration preoperatively . Concurrent medication/care: Subjects received analgesia via PCA pump (fentanyl 1.0 µg·kg–1 iv on each demand with lockout interval of 5 min). (n=20) Intervention 2: Opioid only. received two capsules of matching placebo two hours before scheduled surgery and two capsules of placebo through a nasogastric tube after surgical incision.. Duration preoperatively. Concurrent medication/care: Subjects received analgesia via PCA pump (fentanyl 1.0 µg·kg–1 iv on each demand with lockout interval of 5 min).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score 6 hours at 6 hours postoperatively; Group 1: mean 2.95 pain score (SD 1.252); n=40, Group 2: mean 5 pain score (SD 1); n=20; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 24 hours at 24 hours postoperatively; Group 1: mean 2.55 pain score (SD 1.8835); n=40, Group 2: mean 3.9 pain score (SD 1); n=20; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Fentanyl consumption at 24 hours postoperatively; Group 1: mean 593.65 Micrograms (SD 234.59); n=40, Group 2: mean 924.7 Micrograms (SD 417.5); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at postoperatively; Group 1: 6/40, Group 2: 3/20

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 2/40, Group 2: 2/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Somnolence at postoperatively; Group 1: 3/40, Group 2: 1/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Prutitus at postoperatively; Group 1: 2/40, Group 2: 2/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Headache at postoperatively; Group 1: 1/40, Group 2: 0/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Light headedness at postoperatively; Group 1: 3/40, Group 2: 0/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Pandey 2006[963]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=260)
Countries and setting	Conducted in India; Setting: Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA physical status I and II, of both sexes scheduled for elective laparoscopic cholecystectomy

Exclusion criteria	body weight more than 20% of the ideal body weight; those older than 60 years or younger than 18 years or smokers; history of drug or alcohol abuse; history of hypersensitivity to any drug, history of peptic ulcer disease or of bleeding diathesis or patients taking antacids; impaired kidney or liver functions; patients who had received antiemetics within 24 hr before scheduled surgery or received sedatives other than those determined by protocol, menstruating, pregnant or lactating females, patients who had history of motion sickness, patients on anti-depressants or calcium channels blockers or patients on whom laparoscopic cholecystectomy was converted into open cholecystectomy
Recruitment/selection of patients	scheduled for elective laparoscopic cholecystectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 42.8 ± 11.4; Placebo: 41.8 ± 11.1. Gender (M:F): Define. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 42.8 ± 11.4; Placebo: 41.8 ± 11.1). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (laparoscopic cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=130) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Received 600 mg of gabapentin 2 hours before surgery. Duration preoperatively. Concurrent medication/care: Patients received patient-controlled-analgesia for their pain management (PCA pump was set to fentanyl 1.0 mg/kg patient's activated dose with lockout interval of 10 minutes). Patients received ondansetron 4 mg intravenously when they demanded antiemetics. . Indirectness: No indirectness (n=130) Intervention 2: Opioid only. placebo capsules 2 hours before surgery. Duration preoperatively. Concurrent medication/care: Patients received patient-controlled-analgesia for their pain management (PCA pump was set to fentanyl 1.0 mg/kg patient's activated dose with lockout interval of 10 minutes). Patients received ondansetron 4 mg intravenously when they demanded antiemetics. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Fentanyl consumption at 24 hours postoperatively; Group 1: mean 221.2 Micrograms (µg) (SD 92.4); n=125, Group 2: mean 505.9 Micrograms (µg) (SD 82); n=125; Comments: p value < 0.01
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Surgery converted to open; Group 2 Number missing: 5, Reason: Surgery converted to open Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Postoperative nausea and vomiting at postoperatively; Group 1: 46/125, Group 2: 75/125; Comments: p value 0.04 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Surgery converted to open; Group 2 Number missing: 5, Reason: Surgery converted to open - Actual outcome: Somnolence at postoperatively; Group 1: 4/125, Group 2: 2/125 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Surgery converted to open; Group 2 Number missing: 5, Reason: Surgery converted to open - Actual outcome: Pruritis at postoperatively; Group 1: 1/125, Group 2: 3/125 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Surgery converted to open; Group 2 Number missing: 5, Reason: Surgery converted to open - Actual outcome: Headache at postoperatively; Group 1: 2/125, Group 2: 0/125 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Surgery converted to open; Group 2 Number missing: 5, Reason: Surgery converted to open	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Paulus Lalenoh 2014[567]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=52)
Countries and setting	Conducted in Uganda; Setting: Professor Kandou Hospital Manado
Line of therapy	1st line

Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	not specified
Exclusion criteria	not specified
Recruitment/selection of patients	scheduled for hysterectomy
Age, gender and ethnicity	Age - Mean (range): Pregabalin: 41.7; Placebo: 40.7 - Range (36-48). Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 41.7; Placebo: 40.7 - Range (36-48)). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: gynae-oncology (Hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. 1 hour before surgery pregabalin given 3 mg/kg orally. Duration preoperatively. Concurrent medication/care: Both groups postoperative analgesic morphine given iv injection in Patient Controlled Analgesia (PCA) with the help of PCA infuser.. Indirectness: No indirectness (n=26) Intervention 2: Opioid only. 1 hour before surgery was given a placebo in the form of starch glucose (in the same form with the pregabalin capsules) orally. Duration preoperatively. Concurrent medication/care: Both groups postoperative analgesic morphine given iv injection in Patient Controlled Analgesia (PCA) with the help of PCA infuser.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score 1 hour postoperatively at 1 hour postoperatively; Median (IQR): Pregabalin: 40 (30-50); Placebo: 55 (40-75) visual analogue scale 0-100 Top=High is poor outcome, Comments: p value 0;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: pain score 24 hour postoperatively at 24 hour postoperatively; median (IQR): Pregabalin: 20 (20-40); Placebo: 30 (20-40) pain score

visual analogue scale 0-100 Top=High is poor outcome, Comments: p value 0.003; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 2: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Morphine consumption 24 hours at 24 hour postoperatively; Median (IQR): Pregabalin: 7mg (5-10); Placebo: 10mg (6-15) milligrams, Comments: p value < 0.05); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Radhakrishnan 2005[1024]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in India; Setting: Tertiary University Hospital, New Delhi, India
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18-65, ASA I or II, undergoing elective lumbar laminectomy and discectomy
Exclusion criteria	patients unable to cooperate/ understand the operation of the PCa device, known allergy to gabapentin or morphine, history of drug or alcohol abuse, intake of NSAIDs within 24 hours prior to operation and pregnancy
Recruitment/selection of patients	scheduled lumbar laminectomy and discectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 39.63±10.87; Placebo: 41.67±12.06. Gender (M:F): 40/20. Ethnicity: NA

Further population details	1. Age: <60 years (Gabapentin: 39.63±10.87; Placebo: 41.67±12.06). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: ortho/large joint replacement (lumbar laminectomy and discectomy).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 400mg of Gabapentin the night before surgery and two hours prior to surgery. Duration preoperative. Concurrent medication/care: At arrival in ICU, patients were given a bolus dose of morphine (0.08-0.1mg / kg) through a PCA device. The incremental dose was set at 0.02-0.03mg/kg with a lockout interval of 10 minutes. No background infusion was started. For pain during the lock out interval, the same dose was given as a bolus by the observer. . Indirectness: No indirectness (n=30) Intervention 2: Opioid only. Placebo capsule taken the night before surgery and 2 hours prior to procedure. Duration preoperative. Concurrent medication/care: At arrival in ICU, patients were given a bolus dose of morphine (0.08-0.1mg / kg) through a PCA device. The incremental dose was set at 0.02-0.03mg/kg with a lockout interval of 10 minutes. No background infusion was started. For pain during the lock out interval, the same dose was given as a bolus by the observer. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score <6 hours at <6 hours postoperatively; Median (range) Pain score: Gabapentin: 2 (0-6); Placebo 2 (0-7) pain score visual analogue scale 0-10 Top=High is poor outcome, Comments: p value 0.41;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: pain score 8 hours at 8 hours postoperatively; Median (range) Pain score: Gabapentin: 1 (0-4); Placebo: 1 (0-5) visual analogue scale 0-10 Top=High is poor outcome, Comments: p value 0.42;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Total morphine consumption at ≤8 hours postoperatively; Group 1: mean 20.9 milligrams (SD 9.6); n=30, Group 2: mean 20.5 milligrams (SD 9.26); n=30; Comments: p value 0.88

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at postoperatively; Group 1: 6/30, Group 2: 6/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Vomiting at postoperatively; Group 1: 2/30, Group 2: 3/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Urinary Retention at postoperatively; Group 1: 8/30, Group 2: 7/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Dry mouth at postoperatively; Group 1: 1/30, Group 2: 0/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Somnolance at postoperatively; Group 1: 1/30, Group 2: 1/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pruritis at postoperatively; Group 1: 0/30, Group 2: 2/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Headache at postoperatively; Group 1: 0/30, Group 2: 3/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission
Study	Routray 2018[1073]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=75)
Countries and setting	Conducted in India; Setting: Department of Anaesthesiology and Critical Care, SCB Medical College Hospital, Odisha, India
Line of therapy	1st line

Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA grade I and II of either sex and of age group between 25 and 70 years. All cases were scheduled for elective spine surgery which includes lumbar discectomy and spinal tumor surgeries under general anesthesia
Exclusion criteria	Patients with epilepsy, impaired liver and renal function, history of drug or alcohol abuse, allergy to gabapentin
Recruitment/selection of patients	All cases were scheduled for elective spine surgery which includes lumbar discectomy and spinal tumor surgeries under general anesthesia.
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 35.36 ± 9.97; Pregabalin: 36.56 ± 9.82. Gender (M:F): 21/29. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 35.36 ± 9.97; Pregabalin: 36.56 ± 9.82). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: ortho/large joint replacement (elective spine surgery which includes lumbar discectomy and spinal tumor).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. two gabapentin capsules 300mg each with a sip of water 1 hour before the expected time of induction of anesthesia. Duration preoperatively. Concurrent medication/care: Resule analgesia was Tramadol injection of 1.5mg/kg when the VAS score was more than 4 (n=25) Intervention 2: Opioid plus neuropathic nerve stabiliser - Pregabalin. two pregabalin capsules 150mg each with a sip of water 1 hour before the expected time of induction of anesthesia. Duration preoperatively. Concurrent medication/care: Rescue analgesia was Tramadol injection of 1.5mg/kg when the VAS score was more than 4. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PREGABALIN

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Amount of additional Tramadol used at 24 hours postoperatively: Group 1: mean 190.52 milligrams (mg) (SD 14.8); n=25, Group 2: mean 124.72

milligrams (mg) (SD 9.2); n=25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Sedation at 24 hours postoperatively; Group 1: 5/25, Group 2: 5/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Dizziness at 24 hours postoperatively; Group 1: 5/25, Group 2: 4/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Nausea at 24 hours postoperatively; Group 1: 3/25, Group 2: 2/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at 24 hours postoperatively; Group 1: 4/25, Group 2: 4/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Routray 2018[1073]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=75)
Countries and setting	Conducted in India; Setting: Department of Anaesthesiology and Critical Care, SCB Medical College Hospital, Odisha, India
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	ASA grade I and II of either sex and of age group between 25 and 70 years. All cases were scheduled for elective spine surgery which includes lumbar discectomy and spinal tumor surgeries under general anesthesia
Exclusion criteria	Patients with epilepsy, impaired liver and renal function, history of drug or alcohol abuse, allergy to gabapentin
Recruitment/selection of patients	All cases were scheduled for elective spine surgery which includes lumbar discectomy and spinal tumor surgeries under general anesthesia.
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 35.36 ± 9.97; Pregabalin: 36.56 ± 9.82. Gender (M:F): 21/29. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 35.36 ± 9.97; Pregabalin: 36.56 ± 9.82). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: ortho/large joint replacement (elective spine surgery which includes lumbar discectomy and spinal tumor).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. two gabapentin capsules 300mg each with a sip of water 1 hour before the expected time of induction of anesthesia. Duration preoperatively. Concurrent medication/care: Resule analgesia was Tramadol injection of 1.5mg/kg when the VAS score was more than 4 (n=25) Intervention 2: Opioid plus neuropathic nerve stabiliser - Pregabalin. two pregabalin capsules 150mg each with a sip of water 1 hour before the expected time of induction of anesthesia. Duration preoperatively. Concurrent medication/care: Rescue analgesia was Tramadol injection of 1.5mg/kg when the VAS score was more than 4. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PREGABALIN

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Amount of additional Tramadol used at 24 hours postoperatively; Group 1: mean 190.52 milligrams (mg) (SD 14.8); n=25, Group 2: mean 124.72 milligrams (mg) (SD 9.2); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)

- Actual outcome: Sedation at 24 hours postoperatively; Group 1: 5/25, Group 2: 5/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Dizziness at 24 hours postoperatively; Group 1: 5/25, Group 2: 4/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Nausea at 24 hours postoperatively; Group 1: 3/25, Group 2: 2/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at 24 hours postoperatively; Group 1: 4/25, Group 2: 4/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Said-Ahmed 2007[1092]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=80)
Countries and setting	Conducted in Egypt; Setting: Faculty of Medicine, Ain - Shams University, Cairo, Egypt
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA 1 and 2, scheduled for elective myomectomy
Exclusion criteria	known allergy to gabapentin, history of drug or alcohol abuse, chronic pain or daily intake of analgesics, impaired kidney function
Recruitment/selection of patients	scheduled for elective myomectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 37.33 ± 6.68; Placebo: 36 ± 7. Gender (M:F): all female. Ethnicity: NA

Further population details	1. Age: <60 years (Gabapentin: 37.33 ± 6.68; Placebo: 36 ± 7). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 (ASA I - 68/ ASA II - 12). 3. Type of surgery: gynae-oncology (Myomectomy).
Indirectness of population	--
Interventions	(n=60) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 2 hours before surgery patients received Gabapentin (300, 60, or 1200mg). Duration preoperatively. Concurrent medication/care: Patients received fentanyl 2 mcg/kg on demand.. Indirectness: No indirectness (n=20) Intervention 2: Opioid only. placebo given orally 2 hours before surgery. Duration preoperatively. Concurrent medication/care: Patients received fentanyl 2 mcg/kg on demand.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score 6 hours at 6 hours postoperatively; Group 1: mean 2.6 pain score (SD 1.34); n=60, Group 2: mean 4.2 pain score (SD 1.1); n=20; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: pain score 24 hours at 24 hours postoperatively; Group 1: mean 1.6 pain score (SD 0.84); n=60, Group 2: mean 2.5 pain score (SD 1.2); n=20; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Fentanyl consumption at 24 hours postoperatively; Group 1: mean 236.67 micrograms (SD 91.64); n=60, Group 2: mean 340 micrograms (SD 95); n=20
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at postoperatively; Group 1: 12/60, Group 2: 5/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vomiting at postoperatively; Group 1: 10/60, Group 2: 5/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Dizziness at postoperatively; Group 1: 12/60, Group 2: 3/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Somnolence at postoperatively; Group 1: 8/60, Group 2: 2/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Siddiqui 2014[1141]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=82)
Countries and setting	Conducted in Canada
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with an established diagnosis of IBD between 18 - 60 scheduled for open bowel surgery with a midline incision
Exclusion criteria	Known allergies or sensitivity to morphine or gabapentin, a history of substance abuse or dependence including ethanol (an average of 3 alcoholic beverages or more per day) and marijuana (any amount in the past 3 months), a history of a preexisting seizure or major psychiatric disorder, chronic opioid treatment (more than twice a week for more than 3 months), or limited understanding of the English language.
Recruitment/selection of patients	scheduled for open bowel surgery with a midline incision
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 38.1 ± 12.6; Placebo 37.2 ± 13.2. Gender (M:F): 38/34. Ethnicity: NA

Further population details	1. Age: <60 years (Gabapentin: 38.1 ± 12.6; Placebo 37.2 ± 13.2). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable 3. Type of surgery: lower and upper GI (open bowel surgery with a midline incision).
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 600mg of oral Gabapentin 1 hour before surgery. Duration preoperatively. Concurrent medication/care: Morphine PCA with a bolus of 1.5mg morphien with a lockout of 5 minutes, and a 4 hour limit of 40mg. Inadequate postoperative pain control with this regimen was treated by increasing the bolus, and if needed the 4 hour limit. If in the pain physicians judgment the pain was not adequately controlled with morphine, they would be switched to hydromorphone PCA in equipotent dose settings. . Indirectness: No indirectness (n=41) Intervention 2: Opioid only. Placebo capsules 1 hour before surgery. Duration preoperatively. Concurrent medication/care: Morphine PCA with a bolus of 1.5mg morphine with a lockout of 5 minutes, and a 4 hour limit of 40mg. Inadequate postoperative pain control with this regimen was treated by increasing the bolus, and if needed the 4 hour limit. If in the pain physicians judgment the pain was not adequately controlled with morphine, they would be switched to hydromorphone PCA in equipotent dose settings. . Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at postoperatively; Group 1: 17/36, Group 2: 17/36; Comments: p value 1.0
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: lost to follow up; discontinue intervention; Group 2 Number missing: 5, Reason: lost to follow up; discontinue intervention
- Actual outcome: Vomiting at postoperatively; Group 1: 5/36, Group 2: 6/36; Comments: p value 0.7432
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: lost to follow up; discontinue intervention; Group 2 Number missing: 5, Reason: lost to follow up; discontinue intervention
- Actual outcome: Urinary Retention at postoperatively; Group 1: 2/36, Group 2: 1/36
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: lost to follow up; discontinue intervention; Group 2 Number missing: 5, Reason: lost to follow up; discontinue intervention
- Actual outcome: Somnolence (Drowsiness) at postoperatively; Group 1: 28/36, Group 2: 38/36

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: lost to follow up; discontinue intervention; Group 2 Number missing: 5, Reason: lost to follow up; discontinue intervention - Actual outcome: Pruritis at postoperatively; Group 1: 24/36, Group 2: 23/36; Comments: p value 0.8045 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: lost to follow up; discontinue intervention; Group 2 Number missing: 5, Reason: lost to follow up; discontinue intervention - Actual outcome: Dry mouth at postoperatively; Group 1: 36/36, Group 2: 36/36 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: lost to follow up; discontinue intervention; Group 2 Number missing: 5, Reason: lost to follow up; discontinue intervention - Actual outcome: headache at postoperatively; Group 1: 5/36, Group 2: 7/36; Comments: p value 0.5271 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: lost to follow up; discontinue intervention; Group 2 Number missing: 5, Reason: lost to follow up; discontinue intervention - Actual outcome: Light-headed at postoperatively; Group 1: 22/36, Group 2: 23/36 Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Soltanzadeh 2011[1178]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Iran; Setting: University of Medical Sciences, Ahwaz, Iran
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	20-70 years who were candidates for coronary artery bypass graft (CABG) surgery

Exclusion criteria	history of chronic use of analgesics (nonsteroidal anti-inflammatory drugs, opioids, or paracetamol), tranquilizer, anticonvulsant or anti- depressant drugs; alcohol dependence; malabsorption; hepatic or renal insufficiency; emergency surgery; previous cardiac surgery; left ventricular dysfunction (ejection fraction <40%); pre-operative use of inotropic agents or intra-aortic balloon pump; and allergy to the drugs used in this study. Patients who needed a redo sternotomy were also excluded from the study.
Recruitment/selection of patients	candidates for coronary artery bypass graft (CABG) surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 58.2±8.3; Placebo: 55.2±8.1. Gender (M:F): all male. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 58.2±8.3; Placebo: 55.2±8.1). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (coronary artery bypass graft).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 800 mg oral gabapentin two hours before the surgery, followed by 400 mg oral gabapentin two hours after extubation.. Duration pre and postoperative. Concurrent medication/care: All patients received intramuscular morphine 10 mg and 25 mg promethazine before transferring to the operating room. Postoperatively, 2 mg morphine was administered intra- venously if requested by the patient (NRS≥3) as rescue analgesia.. Indirectness: No indirectness (n=30) Intervention 2: Opioid only. oral placebo two hours before the surgery, followed by placebo two hours after extubation.. Duration pre and postoperative. Concurrent medication/care: All patients received intramuscular morphine 10 mg and 25 mg promethazine before transferring to the operating room. Postoperatively, 2 mg morphine was administered intra- venously if requested by the patient (NRS≥3) as rescue analgesia.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine consumption 24 hours at 24 hours postoperatively; Group 1: mean 2.5 milligrams (SD 0.9); n=30, Group 2: mean 4 milligrams (SD 1.5); n=30; Comments: p value 0.01
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Spreng 2011[1186]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Norway; Setting: Oslo University Hospital, Norway
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for an elective lumbar single level microdiscectomy
Exclusion criteria	<18; ASA >III; known heart, liver, kidney, or psychiatric disease; regular use of opioids; pregnant or breast feeding
Recruitment/selection of patients	Patients scheduled for an elective lumbar single level microdiscectomy
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 44.1 ±10.8; Placebo: 42.9 ± 7.6. Gender (M:F): 24/22. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 44.1 ±10.8; Placebo: 42.9 ± 7.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (all patients ASA I or II). 3. Type of surgery: ortho/large joint replacement (lumbar single level microdiscectomy).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. 150mg Pregabalin one hour before surgery. Duration preoperatively. Concurrent medication/care: All patients were pre-medicated with Paracetamol (<60kg - 1000mg; >60kg - 1500mg). Postoperatively patients equipped with IV PCA for the first 24 hours, 2mg morphine bolus with a 10 minute lock out time. . Indirectness: No indirectness (n=25) Intervention 2: Opioid only. dose/quantity, brand name, extra details. Duration preoperatively. Concurrent medication/care: All patients were pre-medicated with Paracetamol (<60kg - 1000mg; >60kg -

	1500mg). Postoperatively patients equipped with IV PCA for the first 24 hours, 2mg morphine bolus with a 10 minute lock out time. . Indirectness: No indirectness
Funding	Other (Study financed by Institutional means)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: VAS pain at rest (Mean area under the curve) at 30 - 240 minutes postoperatively ; Mean Area Under the curve (AUC): Pregabalin: 3227 ± 2037; Placebo: 4930 ± 2279 visual analogue scale 0-100 Top=High is poor outcome, Comments: p value 0.011;
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea at postoperatively; Group 1: 7/22, Group 2: 14/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear
- Actual outcome: Vomiting at postoperatively; Group 1: 2/22, Group 2: 1/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear
- Actual outcome: Sedation at postoperatively; Group 1: 3/22, Group 2: 2/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear
- Actual outcome: Dizziness at postoperatively; Group 1: 2/22, Group 2: 5/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear
- Actual outcome: Pruritis at postoperatively; Group 1: 1/22, Group 2: 7/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear
- Actual outcome: Urinary Retention at postoperatively; Group 1: 5/22, Group 2: 5/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear
- Actual outcome: Respiratory Depression at postoperatively; Group 1: 2/22, Group 2: 0/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear
- Actual outcome: Headache at postoperatively; Group 1: 2/22, Group 2: 2/24
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 1, Reason: Unclear	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Srivastava 2010[1188]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=127)
Countries and setting	Conducted in India; Setting: S N Medical College, Uttar Pradesh, India
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA status I and II patients requiring elective minilap open cholecystectomy
Exclusion criteria	Any patient having body weight more than 20% of ideal weight or uncontrolled systemic disease (asthma, hypertension, diabetes, renal insufficiency, cardiac and liver disease), having a history of drug or alcohol abuse and who could not show adequate skill to use patient- controlled analgesia (PCA) pump were excluded from the study.
Recruitment/selection of patients	scheduled for open cholecystectomy
Age, gender and ethnicity	Age - Mean (SD): gabapentin: 43±7.06; Placebo: 44.7±9.40. Gender (M:F): 38/82. Ethnicity: NA
Further population details	1. Age: <60 years (gabapentin: 43±7.06; Placebo: 44.7±9.40). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (open cholecystectomy).
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 600mg of gabapentin orally with sips of water 2h before surgery. Duration preoperatively. Concurrent medication/care: all the patients received a bolus dose of 50mg of tramadol followed by 20mg on demand with a lockout interval of 15min with a maximum allowable dose of 240mg in 4 h.. Indirectness: No indirectness

	(n=64) Intervention 2: Opioid only. identical looking capsule placebo orally with sips of water 2h before surgery. Duration preoperatively. Concurrent medication/care: all the patients received a bolus dose of 50mg of tramadol followed by 20mg on demand with a lockout interval of 15min with a maximum allowable dose of 240mg in 4 h.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Tramadol consumption at 24 hours postoperatively; Group 1: mean 253.9 milligrams (SD 44.8); n=60, Group 2: mean 375.8 milligrams (SD 83.5); n=60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: PCA malfunction; altered surgery; Group 2 Number missing: 4, Reason: PCA malfunction; altered surgery

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Sedation at Postoperatively; Group 1: 14/60, Group 2: 8/60; Comments: P value < 0.05
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: PCA malfunction; altered surgery; Group 2 Number missing: 4, Reason: PCA malfunction; altered surgery
- Actual outcome: Nausea and Vomiting at Postoperatively; Group 1: 15/60, Group 2: 31/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: PCA malfunction; altered surgery; Group 2 Number missing: 4, Reason: PCA malfunction; altered surgery
- Actual outcome: Dizziness at Postoperatively; Group 1: 5/60, Group 2: 7/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: PCA malfunction; altered surgery; Group 2 Number missing: 4, Reason: PCA malfunction; altered surgery
- Actual outcome: Respiratory depression at Postoperatively; Group 1: 0/60, Group 2: 1/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: PCA malfunction; altered surgery; Group 2 Number missing: 4, Reason: PCA malfunction; altered surgery
- Actual outcome: Pruritus at Postoperatively; Group 1: 4/60, Group 2: 3/60
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: PCA malfunction; altered surgery; Group 2 Number missing: 4,

Reason: PCA malfunction; altered surgery	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Sundar 2012[1215]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in India; Setting: Sri Ramachandra Medical College, India
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients scheduled for elective Off Pump Coronary Artery Bypass surgery under general anesthesia
Exclusion criteria	1. Ejection fraction of less than 50%. 2. Preoperative left bundle branch block. 3. Known sensitivity to pregabalin. 4. Documented pre-existing chronic pain on or off analgesics. 5. Seizure disorders. 6. Patients who were taking pregabalin or gabapentin. 7. Patients on chronic neuroleptic medications and taking tricyclic antidepressants or serotonin and norepinephrine re-uptake inhibitors. 8. Age more than 70 years. 9. Pregnant or breast-feeding females. 10. Anticipated difficult airway. 11. Severe systemic disorders (e.g., insulin-dependent diabetes mellitus, uncontrolled hypertension,

	kidney or liver insufficiency, and severe respiratory disorder).
Recruitment/selection of patients	scheduled for elective Off Pump Coronary Artery Bypass surgery under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 60.1 ± 8.6; Placebo: 57.2 ± 7.6. Gender (M:F): 42/18. Ethnicity: NA
Further population details	1. Age: >60 years (Pregabalin: 60.1 ± 8.6; Placebo: 57.2 ± 7.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. Type of surgery: Not applicable (Elective Off Pump Coronary Artery Bypass).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. 150 mg of pregabalin orally 60 min before surgery. Duration preoperatively. Concurrent medication/care: Postoperatively fentanyl 0.5 mcg/kg was given whenever visual analog scale (VAS) was 4 or more. From the first postoperative day onward all of the patients received the following medications routinely: Enoxaparin 40 mg/day subcutaneously, clopidogrel 75 mg/day, aspirin 75 mg/day, to inhibit platelet aggregation, and 20 mg/day pantoprazole for gastric protection.. Indirectness: No indirectness (n=30) Intervention 2: Opioid only. placebo capsule similar to pregabalin, 60 minutes before surgery. Duration preoperatively. Concurrent medication/care: Postoperatively fentanyl 0.5 mcg/kg was given whenever visual analog scale (VAS) was 4 or more. From the first postoperative day onward all of the patients received the following medications routinely: Enoxaparin 40 mg/day subcutaneously, clopidogrel 75 mg/day, aspirin 75 mg/day, to inhibit platelet aggregation, and 20 mg/day pantoprazole for gastric protection.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score 6 hours at 6 hours postoperatively; Group 1: mean 2.03 pain score (SD 0.61); n=30, Group 2: mean 2.2 pain score (SD 0.61); n=30; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.296

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 24 hours at 24 hours postoperatively; Group 1: mean 2.07 pain score (SD 0.74); n=30, Group 2: mean 2 pain score (SD 0.64); n=30; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.711

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Amount of additional medication use (>6-24 hours post op) - Actual outcome: Fentanyl consumption at 24 hours postoperatively; Group 1: mean 241.67 Micrograms (SD 178.87); n=30, Group 2: mean 251.67 Micrograms (SD 181.47); n=30; Comments: p value 0.638 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Vomiting at Postoperatively; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Dizziness at Postoperatively; Group 1: 0/30, Group 2: 0/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Syal 2010[1227]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=120)
Countries and setting	Conducted in India; Setting: Indira Gandhi Hospital, Shimla
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	ASA I and II, 20 to 50 years, weighing between 40 to 65 kg and undergoing elective surgery (open cholecystectomy) under general anesthesia.
Exclusion criteria	Patients on chronic analgesic therapy, MAO inhibitor therapy, corticosteroids or taking any other drugs acting on central nervous system, patients suffering from nausea/ vomiting, pregnant or lactating patients and patients with known allergy to Gabapentin were excluded from study.
Recruitment/selection of patients	patients undergoing open cholecystectomy under general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 39.97 ± 6.20; Placebo: 39.60 ± 7.69. Gender (M:F): Unclear. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 39.97 ± 6.20; Placebo: 39.60 ± 7.69). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: lower and upper GI (open cholecystectomy).
Indirectness of population	--
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Patients received 1200 mg of Gabapentin packed in 5 capsules.. Duration Unclear. Concurrent medication/care: Injection Tramadol 1mg kg-1 was given over 2-3 minutes intravenously and after a further 30 minutes VAS was observed. Further increment of 20 mg was given if VAS = 40m and the total dose (maximum 400 mg/24 hours) were recorded.. Indirectness: No indirectness (n=30) Intervention 2: Opioid only. Patients received 5 placebo capsules filled with thin sugar. Duration Unclear. Concurrent medication/care: Injection Tramadol 1mg kg-1 was given over 2-3 minutes intravenously and after a further 30 minutes VAS was observed. Further increment of 20 mg was given if VAS = 40mm and the total dose (maximum 400 mg/24 hours) were recorded.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Tramadol consumption at 24 hours postoperatively; Group 1: mean 106.33 milligrams (SD 32.07); n=30, Group 2: mean 203.83 milligrams (SD 41.55); n=30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Nausea and Vomiting at Postoperatively; Group 1: 25/30, Group 2: 14/30
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0 - Actual outcome: Sedation at Postoperatively; Group 1: 30/30, Group 2: 29/30 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Tuncer 2005[1274]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=45)
Countries and setting	Conducted in Turkey; Setting: University of Selcuk, Turkey
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II scheduled to undergo major orthopaedic surgery with general anesthesia
Exclusion criteria	<18 or >65, weight <50 or >100kg, known allergy to morphine or gabapentin, use of NSAID or opioids in the 24h preceding surgery, inability to understand pain scales or use a PCA device.
Recruitment/selection of patients	scheduled to undergo major orthopaedic surgery with general anesthesia
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 37.05 ± 16.04; Placebo: 37.8 ± 16.6. Gender (M:F): not specified. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 37.05 ± 16.04; Placebo: 37.8 ± 16.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: ortho/large joint replacement (Major orthopaedic surgery).
Indirectness of population	No indirectness

Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. Received Gabapentin (1200mg or 800mg) 1 hour before surgery. Duration Preoperatively. Concurrent medication/care: PCA morphine set to deliver morphine 1mg in a 1ml solution on demand. The lockout interval was set to 7 minutes. (n=15) Intervention 2: Opioid only. Placebo capsule given 1 hour before surgery. Duration preoperatively. Concurrent medication/care: PCA morphine set to deliver morphine 1mg in a 1ml solution on demand. The lockout interval was set to 7 minutes.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: pain score at 4 hours at 4 hours postoperatively; Group 1: mean 1.9 pain score (SD 2.266); n=30, Group 2: mean 2.4 pain score (SD 1.7); n=15; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Morphine consumption at 4 hours at 4 hours postoperatively; Group 1: mean 13.45 milligrams (SD 5.773); n=30, Group 2: mean 21.4 milligrams (SD 5.9); n=15
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Nausea at < 4 hours postoperatively; Group 1: 12/30, Group 2: 6/15
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Vomiting at < 4 hours postoperatively; Group 1: 3/30, Group 2: 2/15
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Dizziness at < 4 hours postoperatively; Group 1: 14/30, Group 2: 7/15
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Headache at < 4 hours postoperatively; Group 1: 7/30, Group 2: 4/15
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Turan 2004[1275]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Turkey; Setting: Trakya University Medical Faculty, Turkey
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	≥18 yr old, weighed more than 40 kg, and could operate a patient-controlled analgesia (PCA) device
Exclusion criteria	known allergy, sensitivity, asthma, contraindications to morphine or any other study drug, renal insufficiency, history of peptic ulcer or of bleeding diathesis, use of narcotic analgesics or gabapentin, and pregnancy.
Recruitment/selection of patients	scheduled for elective lumbar discectomy or spinal fusion surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 48 ± 9; Placebo: 45 ± 8 yr. Gender (M:F): 28/22. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 48 ± 9; Placebo: 45 ± 8 yr). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I or II). 3. Type of surgery: ortho/large joint replacement (elective lumbar discectomy or spinal fusion surgery).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 1,200 mg gabapentin 1 hour before surgery. Duration preoperatively. Concurrent medication/care: All patients received 1 mg/ml morphine via the PCA with an incremental dose of 2 mg, a lockout interval of 10 min, and a 4-h limit of 40 mg. The incremental dose was increased to 3 mg, and the 4-h limit to 50 mg, if analgesia was inadequate after 1 h.

	(n=25) Intervention 2: Opioid only. Oral placebo 1 hour before surgery. Duration preoperatively . Concurrent medication/care: All patients received 1 mg/ml morphine via the PCA with an incremental dose of 2 mg, a lockout interval of 10 min, and a 4-h limit of 40 mg. The incremental dose was increased to 3 mg, and the 4-h limit to 50 mg, if analgesia was inadequate after 1 h. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score < 6 hours postoperatively at < 6 hours postoperatively; Median (IQR): Gabapentin: 0(0–2); Placebo: 2 (0–4) 0-10 visual analogue scale Top=High is poor outcome;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Pain score 24 hours postoperatively at 24 hours postoperatively; Median (IQR): Gabapentin: 0 (0–2); Placebo: 0 (0–3) visual analogue scale 0-10 Top=High is poor outcome;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Morphine consumption 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 3.8 Milligrams (SD 4.6); n=25, Group 2: mean 11.4 Milligrams (SD 5.4); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Morphine consumption < 6 hours postoperatively at 6 hours postoperatively; Group 1: mean 2.4 Milligrams (SD 1.8); n=25, Group 2: mean 6.4 Milligrams (SD 4.3); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Dizziness at Postoperatively; Group 1: 6/25, Group 2: 4/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Nausea at Postoperatively; Group 1: 5/25, Group 2: 7/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Vomiting at Postoperatively; Group 1: 1/25, Group 2: 6/25

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Somnolence at Postoperatively; Group 1: 2/25, Group 2: 1/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pruritus at Postoperatively; Group 1: 1/25, Group 2: 2/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Urinary Retention at Postoperatively; Group 1: 0/25, Group 2: 5/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Turan 2004[1276]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Turkey; Setting: Trakya University, Turkey
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 yr old, weighed more than 40 kg, and could operate a PCA device
Exclusion criteria	known allergy to opioids, asthma, contraindications to tramadol or any drug used, renal insufficiency, a history of a peptic ulcer or a history of a bleeding diathesis.
Recruitment/selection of patients	undergoing elective total abdominal hysterectomy with salpingo-oophorectomy

Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 52.5 ± 11.2; Placebo: 50.4 ± 10.2. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 52.5 ± 11.2; Placebo: 50.4 ± 10.2). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 1 (ASA I: 40; ASA II: 10). 3. Type of surgery: gynae-oncology (total abdominal hysterectomy with salpingo-oophorectomy).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 1200 mg gabapentin 1 hour before surgery. Duration preoperatively. Concurrent medication/care: All patients received tramadol PCA (3 mg/mL) with an initial 50 mg loading dose, 20 mg incremental dose, 10-min lockout interval, and 4-h limit of 300 mg. The incremental dose was increased to 30 mg if analgesia was inadequate after 1 h. . Indirectness: No indirectness (n=25) Intervention 2: Opioid only. Oral placebo capsules 1 hour before surgery . Duration Preoperatively. Concurrent medication/care: All patients received tramadol PCA (3 mg/mL) with an initial 50 mg loading dose, 20 mg incremental dose, 10-min lockout interval, and 4-h limit of 300 mg. The incremental dose was increased to 30 mg if analgesia was inadequate after 1 h. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score < 6 hours postoperatively at < 6 hours postoperatively; Group 1: mean 1.8 pain score (SD 1.6); n=25, Group 2: mean 4.2 pain score (SD 1); n=25; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Pain score 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 0.5 pain score (SD 0.7); n=25, Group 2: mean 1.6 pain score (SD 1.2); n=25; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Tramadol consumption < 6 hours postoperatively at < 6 hours postoperatively; Group 1: mean 118.3 Milligrams (SD 56.8); n=25, Group 2: mean 120.2 Milligrams (SD 52); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0
- Actual outcome: Tramadol consumption 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 10.1 milligrams (SD 5); n=25, Group 2: mean 28.2 milligrams (SD 4); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0

Protocol outcome 2: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Dizziness at Postoperatively; Group 1: 2/25, Group 2: 1/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Nausea at Postoperatively; Group 1: 5/25, Group 2: 7/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Vomiting at Postoperatively; Group 1: 6/25, Group 2: 9/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Somnolence at Postoperatively; Group 1: 1/25, Group 2: 0/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Pruritus at Postoperatively; Group 1: 0/25, Group 2: 2/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:0 ; Group 2 Number missing: 0 - Actual outcome: Urinary Retention at Postoperatively; Group 1: 1/25, Group 2: 3/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Pain (>6-24 hours post op) ; Amount of additional medication use (< 6 hours post op) ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	Vahedi 2011[1294]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=206)
Countries and setting	Conducted in Iran; Setting: Tertiary University Hospital, Iran
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>18 to ≤60, weight range 60 to 80kg, ASA I or II, and concordant clinical imaging characteristics necessitating the need for laminectomy and discectomy in one single lumbar level.
Exclusion criteria	Primary Exclusion criteria: refusal to provide informed consent, pregnancy, current consumption of gabapentin, alcohol or drug abuse, known hepatic or renal disease, analgesic consumption during the last 24 hours, known allergy to gabapentin, and preoperative decision to perform lumbar fixation technique. Secondary Exclusion Criteria: intraoperative instability making a fusion technique necessary, the extension of laminectomy to more than one level, inability to use PCA, reluctant patient, and complete resolution of pain after the surgery.
Recruitment/selection of patients	Candidates for single level lumbar laminectomy and discectomy
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 44.5 ± 10.374; Placebo: 44.4 ± 10.558. Gender (M:F): 44/32. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 44.5 ± 10.374; Placebo: 44.4 ± 10.558). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not applicable (ASA I or II). 3. Type of surgery: ortho/large joint replacement (single level lumbar laminectomy and discectomy).
Extra comments	There are preoperative exclusion criteria and intra/postoperative exclusion criteria.
Indirectness of population	No indirectness
Interventions	(n=103) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. 300mg Gabapentin 2 hours before surgery. Duration Preoperatively. Concurrent medication/care: Each patient received the first dose of morphine (0.1mg/kg) via a PCA pump and then was transferred to intensive care unit. A similar PCA setting was applied in all patients (lock-out interval time of 20 minutes, bolus infusion of 0.03mg/kg and no maintenance infusion. . Indirectness: No indirectness (n=103) Intervention 2: Opioid only. Identical placebo taken 2 hours before surgery. Duration preoperatively.

	Concurrent medication/care: Each patient received the first dose of morphine (0.1mg/kg) via a PCA pump and then was transferred to intensive care unit. A similar PCA setting was applied in all patients (lock-out interval time of 20 minutes, bolus infusion of 0.03mg/kg and no maintenance infusion. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain scores 6 hours postoperatively at 6 hours postoperatively; Group 1: mean 6.111 pain score (SD 2.094); n=36, Group 2: mean 5.675 pain score (SD 2.443); n=40; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.257
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - As a secondary exclusion criteria patients with complete resolution of pain after the surgery were excluded after the intervention, therefore not included in the analysis.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain scores 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 2.583 pain score (SD 1.948); n=36, Group 2: mean 3.4 pain score (SD 2.716); n=40; visual analogue scale 0-10 Top=High is poor outcome; Comments: p value 0.190
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - As a secondary exclusion criteria patients with complete resolution of pain after the surgery were excluded after the intervention, therefore not included in the analysis.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Morphine Consumption 6 hours postoperatively at 6 hours postoperatively; Group 1: mean 5.333 milligrams (SD 3.207); n=36, Group 2: mean 6.4 milligrams (SD 3.455); n=40; Comments: p value 0.950
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - As a secondary exclusion criteria patients with complete resolution of pain after the surgery were excluded after the intervention, therefore not included in the analysis.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcome 4: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine Consumption 24 hours postoperatively at 24 hours postoperatively; Group 1: mean 3.944 milligrams (SD 3.43); n=36, Group 2: mean 4.1 milligrams (SD 3.761); n=40; Comments: p value 0.083
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - As a secondary exclusion criteria patients with complete resolution of pain after the surgery were excluded after the intervention, therefore not included in the analysis.; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcomes not reported by the study	Quality of life ; Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Waikakul 2011[1324]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=99)
Countries and setting	Conducted in Thailand; Setting: Ramathibodi Hospital, Thailand
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18-80 years, ASA I, II, or III, and personally signed and dated informed consent document.
Exclusion criteria	allergic to the trial drugs and sulfonamides, patient with a history of coagulopathy, thromboembolic event, unstable angina, myocardial, or cerebral infarction within one year prior to operation, and woman with plasma creatinine >100 µmol/L and >115 µmol/L in men. Exclusion included pregnant woman or in lactation period, participation in any other studies, and history of significant alcohol, analgesic, or narcotic substance abuse within six months prior to screening.
Recruitment/selection of patients	Scheduled for major orthopaedic surgery
Age, gender and ethnicity	Age - Mean (SD): Gabapentin: 44.7 ± 19.4; Placebo: 50.4 ± 13.6. Gender (M:F): 31/19. Ethnicity: NA
Further population details	1. Age: <60 years (Gabapentin: 44.7 ± 19.4; Placebo: 50.4 ± 13.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I 16; ASA II 25; ASA III 9). 3. Type of surgery: ortho/large joint replacement (major spinal surgery (decompression or fixation or reconstruction)).
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Opioid plus neuropathic nerve stabiliser - Gabapentin. gabapentin 400 mg one to two hours before anesthesia and then gabapentin 300 mg 12 and 24 hours later.. Duration preoperative and postoperative. Concurrent medication/care: Analgesia if required was initially managed with IV morphine 1-

	2mg every 15 minutes until the pain was relieved. The patient was connected to a PCA On arrival to the wards. Initial setting was patient-controlled dose 1-2 mg, lockout interval eight minutes, and four-hour limit 40 mg. The incremental dose was increased to 2-2.5 mg, and the four-hour limit was increased to 50 mg if analgesia was inadequate after one hour. If analgesia remained inadequate after an additional hour, the incremental dose was further increased to 3.0 mg, and the four-hour limit was increased to 60 mg. care unit (PACU), patient was asked to rate his/her pain every 15 minutes using a numerical rating scale (NRS) ranging from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain. Analgesia, if required, was initially managed with intravenous morphine 1-2 mg every 15 minute until the pain was relieved. The loading dose of morphine was recorded. The patient was connected to a PCA pump (IVAC® (n=28) Intervention 2: Opioid only. Placebo one to two hours before anesthesia and placebo 12 and 24 hours later. Duration preoperative and postoperative. Concurrent medication/care: Analgesia if required was initially managed with IV morphine 1-2mg every 15 minutes until the pain was relieved. The patient was connected to a PCA On arrival to the wards. Initial setting was patient-controlled dose 1-2 mg, lockout interval eight minutes, and four-hour limit 40 mg. The incremental dose was increased to 2-2.5 mg, and the four-hour limit was increased to 50 mg if analgesia was inadequate after one hour. If analgesia remained inadequate after an additional hour, the incremental dose was further increased to 3.0 mg, and the four-hour limit was increased to 60 mg. care unit (PACU), patient was asked to rate his/her pain every 15 minutes using a numerical rating scale (NRS) ranging from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain. Analgesia, if required, was initially managed with intravenous morphine 1-2 mg every 15 minute until the pain was relieved. The loading dose of morphine was recorded. The patient was connected to a PCA pump (IVAC®. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO	

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score 4 hours at < 6 hours postoperatively; Median (IQR): Gabapentin: 5.0 (0-10); Placebo: 6.0 (0-10) pain score numerical rating scale 0-10 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear ; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 24 hours at 24 hours postoperatively; Median (IQR): Gabapentin: 3.0 (0-8); Placebo: 3.5 (0-7) 0-10 numerical rating scale 0-10 Top=;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear ; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Cumulative morphine 4 hours at < 6 hours postoperatively; ;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear ; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 4: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Cumulative morphine 24 hours at 24 hours postoperatively; Median (IQR): Gabapentin: 15.5 (0-37); Placebo: 18 (1-63) milligrams);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear ; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 5: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Itching at 24 hours postoperatively; Group 1: 0/26, Group 2: 2/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear ; Group 2 Number missing: 4, Reason: Unclear
- Actual outcome: Urinary Retention at 24 hours postoperatively; Group 1: 1/26, Group 2: 0/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear ; Group 2 Number missing: 4, Reason: Unclear
- Actual outcome: Dizziness at 24 hours postoperatively; Group 1: 0/26, Group 2: 1/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Unclear ; Group 2 Number missing: 4, Reason: Unclear
- Actual outcome: Somnolence at 24 hours postoperatively; Group 1: 1/26, Group 2: 0/24
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Unclear ; Group 2 Number missing: 4, Reason: Unclear

Protocol outcomes not reported by the	Quality of life ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS))

study	; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**White 2009[1355]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=108)
Countries and setting	Conducted in USA; Setting: University of Texas Southwestern Medical Center at Dallas, Dallas, Texas.
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I–III patients, aged 18–70 yr, scheduled for elective ambulatory and short-stay (<24 h) surgical procedures
Exclusion criteria	Patients were excluded if they were known to be allergic to gabapentin or pregabalin, had any clinically significant medical or psychiatric conditions, were pregnant or lactating, had a history of alcohol or drug abuse within the past 6 mo, or were taking opioid-containing pain or sedative medications on a long-term basis.
Recruitment/selection of patients	scheduled for elective ambulatory and short-stay (<24 h) surgical procedures
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 45.67 ± 14.53; Placebo: 48 ± 15. Gender (M:F): 52/ 53. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 45.67 ± 14.53; Placebo: 48 ± 15). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 20; ASA II 66; ASA III 15). 3. Type of surgery: Not applicable (lective ambulatory and short-stay (<24 h) surgical procedures (e.g., ear–nose–throat, laparoscopic, urologic and plastic surgery)).
Indirectness of population	--
Interventions	(n=81) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. 60–90 min before induction of general anesthesia participants were given Pregabalin (75mg, 150mg, or 300mg) orally. Duration preoperatively. Concurrent medication/care: In the postanesthesia care unit (PACU), fentanyl, 25–50µg (micrograms) IV, boluses were administered to control acute postoperative pain when the patient complained of moderate-to-severe pain.. Indirectness: No indirectness

	(n=27) Intervention 2: Opioid only. oral placebo 60–90 min before induction of general anesthesia.. Duration preoperatively. Concurrent medication/care: In the postanesthesia care unit (PACU), fentanyl, 25–50µg (micrograms) IV, boluses were administered to control acute postoperative pain when the patient complained of moderate-to-severe pain.. Indirectness: No indirectness
Funding	Study funded by industry (Supported, in part, by an unrestricted educational grant from Pfizer (New York, NY), endowment funds from the Margaret Milam McDermott Distinguished Chair in Anesthesiology, and the White Mountain Institute, a nonprofit private foundation (Paul F. White, President).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score 2 hours at < 6 hours postoperatively; Group 1: mean 4 (SD 3.109); n=81, Group 2: mean 4 (SD 3); n=27; verbal rating scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 24 hours at 24 hours postoperatively; Group 1: mean 3.33 (SD 2.43); n=81, Group 2: mean 2 (SD 2); n=27; verbal rating scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Rescue Fentanyl in PACU (<2 hours) at < 6 hours postoperatively; Group 1: mean 85.67 Micrograms (SD 107.1); n=81, Group 2: mean 93 Micrograms (SD 76); n=27
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
- Actual outcome: Dizziness at 2 hours postoperatively; Group 1: 17/81, Group 2: 1/27
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Yucel 2011[1417]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Turkey; Setting: Tertiary Hospital, Turkey
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ASA I or II; 25 - 65 years of age scheduled for elective total abdominal hysterectomy under general anesthesia.
Exclusion criteria	known allergy to opioids or pregabalin, history of cardiovascular, renal or hepatic disease, psychiatric disorders, chronic pain syndromes, drugs or alcohol abuse, and refusal for participation. Patients receiving regular opioids or drugs (acetaminophen, NSAIDs, sedatives, or anticonvulsants) within 24 hours before surgery were also excluded. Patients with systolic arterial blood pressure levels >160 mm Hg or diastolic arterial blood pressure levels >90mm Hg were also excluded.
Recruitment/selection of patients	scheduled for elective total abdominal hysterectomy under general anesthesia.
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 44.84 ± 8.44; Placebo: 42.47 ± 9.31. Gender (M:F): all female. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 44.84 ± 8.44; Placebo: 42.47 ± 9.31). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I: 66/ ASA II: 24). 3. Type of surgery: gynae-oncology (abdominal hysterectomy).
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. receive pregabalin (150mg or 300mg) 4 hours before the induction of anesthesia and at 12 hours postoperatively. . Duration preoperatively and postoperatively. Concurrent medication/care: All the patients received PCA with intravenous morphine and were followed for 24 hours. After administration of 5 mg morphine over 30 minutes, starting 15 minutes

	before the estimated time of completion of surgery, the PCA device was set to deliver 2 mg of morphine with a lockout of 15 minutes and a 4 hour limit of 20 mg, and no continuous infusion. If analgesia was felt to be inadequate at any time during the study, the lockout time was shortened to 5 minutes. . Indirectness: No indirectness (n=30) Intervention 2: Opioid only. receive Placebo 4 hours before the induction of anesthesia and at 12 hours postoperatively. . Duration preoperatively and postoperatively. Concurrent medication/care: All the patients received PCA with intravenous morphine and were followed for 24 hours. After administration of 5 mg morphine over 30 minutes, starting 15 minutes before the estimated time of completion of surgery, the PCA device was set to deliver 2 mg of morphine with a lockout of 15 minutes and a 4 hour limit of 20 mg, and no continuous infusion. If analgesia was felt to be inadequate at any time during the study, the lockout time was shortened to 5 minutes. . Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain (< 6 hours post op)
- Actual outcome: Pain score < 6 hours at < 6 hours postoperatively; Group 1: mean 2.87 pain score (SD 0.33); n=60, Group 2: mean 3.33 pain score (SD 1); n=30; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain (>6-24 hours post op)
- Actual outcome: Pain score 24 hours at 24 hours postoperatively; Group 1: mean 1.52 pain score (SD 0.55); n=60, Group 2: mean 1.73 pain score (SD 0.6); n=30; visual analogue scale 0-10 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Cumulative Morphine consumption 24 hours at 24 hours postoperatively; Group 1: mean 37.3 milligrams (SD 5.9); n=60, Group 2: mean 46.97 milligrams (SD 6.67); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Cumulative Morphine consumption 6 hours at 6 hours postoperatively; Group 1: mean 25.19 milligrams (SD 4.47); n=60, Group 2: mean 32.6 milligrams (SD 5.3); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) - Actual outcome: Ramsay Sedation score 6 hours at 6 hours postoperatively; Group 1: mean 1.59 (SD 0.57); n=60, Group 2: mean 1.27 (SD 0.45); n=30; Ramsauy Sedation score 0-6 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Ramsay Sedation score 24 hours at 24 hours postoperatively; Group 1: mean 1.17 (SD 0.42); n=60, Group 2: mean 1.1 (SD 0.31); n=30; Ramsay Sedation score 0-6 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Nausea and vomiting at postoperatively; Group 1: 7/60, Group 2: 7/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Pruritus at postoperatively; Group 1: 10/60, Group 2: 6/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Dizziness at postoperatively; Group 1: 21/60, Group 2: 8/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Amount of additional medication use (>6-24 hours post op) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Study	**Ziyaeifard 2015[1445]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Iran; Setting: Rajaie Cardiovascular, Medical and Research Center, Tehran, Iran
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	> 20 years of age and ASA I - III
Exclusion criteria	Patients with liver or renal dysfunction, metabolic disorders, and left bundle branch block (LBBB) were excluded from study. In addition, patients with indications of emergency surgical operation, those using opioids, patients with a history of drug sensitivity or seizures, smokers, and those with ejection fraction (EF) < 35% were excluded.
Recruitment/selection of patients	planned for elective CABG with Laryngeal view
Age, gender and ethnicity	Age - Mean (SD): Pregabalin: 54.7 ± 8.3; Placebo: 57.9 ± 8.6. Gender (M:F): 50/10. Ethnicity: NA
Further population details	1. Age: <60 years (Pregabalin: 54.7 ± 8.3; Placebo: 57.9 ± 8.6). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear (ASA I - III). 3. Type of surgery: Not applicable (Coronoary artery bypass graft).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Opioid plus neuropathic nerve stabiliser - Pregabalin. 150mg Pregabalin 2 hours before surgery. Duration preoperatively. Concurrent medication/care: Patients having VAS scores > 3 received 0.1 mg/kg of intravenous morphine up to 8 mg.. Indirectness: No indirectness (n=30) Intervention 2: Opioid only. Placebo 2 hours before surgery. Duration preoperatively. Concurrent medication/care: Patients having VAS scores > 3 received 0.1 mg/kg of intravenous morphine up to 8 mg.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Amount of additional medication use (< 6 hours post op)
- Actual outcome: Morphine usage 4 hours at 4 hours postoperatively; Group 1: mean 5 milligrams (SD 0.2); n=30, Group 2: mean 4.9 milligrams (SD 0.2); n=30; Comments: p value 0.87
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 2: Amount of additional medication use (>6-24 hours post op)
- Actual outcome: Morphine usage 24 hours at 24 hours postoperatively; Group 1: mean 3 milligrams (SD 0.17); n=30, Group 2: mean 3.1 milligrams (SD 0.15); n=30; Comments: p value 0.94
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the	Quality of life ; Pain (< 6 hours post op) ; Pain (>6-24 hours post op) ; Adverse events (including respiratory

study	depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects) ; Psychological distress and mental wellbeing (hospital anxiety and depression scale (HADS)) ; Symptom scores ; Functional measures ; Length of stay in intensive care unit ; Length of hospital stay ; Hospital readmission

Appendix D: Forest plots

D.1 Gabapentin vs Placebo for managing acute post-operative pain

Figure 176: Pain score ≤ 6 hours

Study or Subgroup	Gabapentin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abdelmageed 2010	3.2	0.8	30	2.1	0.6	30	4.6%	1.10 [0.74, 1.46]
Ajori 2012	4	3	69	6.3	2.8	69	3.9%	-2.30 [-3.27, -1.33]
Al-Mujadi 2006	1.4	0.7	37	2.41	1.3	35	4.5%	-1.01 [-1.50, -0.52]
Behdad 2012	3.8	0.96	30	6.62	1.37	31	4.4%	-2.82 [-3.41, -2.23]
Ghafari 2009	4.25	0.35	33	5.81	0.4	33	4.7%	-1.56 [-1.74, -1.38]
Hanoura 2018	1	0.6	19	1.3	0.7	19	4.6%	-0.30 [-0.71, 0.11]
Hassani 2015	2.1	0.3	30	2.3	0.5	30	4.7%	-0.20 [-0.41, 0.01]
Hosseini 2015	1.64	1.02	22	3.09	1.01	22	4.4%	-1.45 [-2.05, -0.85]
Khan 2011	4.35	1.413	150	6.8	1.1	25	4.5%	-2.45 [-2.94, -1.96]
Khan 2013	4.35	0.779	34	6.971	1.2	35	4.5%	-2.62 [-3.10, -2.14]
Marashi 2012	3.6	0.7	22	5.9	0.9	22	4.5%	-2.30 [-2.78, -1.82]
Mardani-Kivi 2013	4.8	2.08	55	6.9	1.86	53	4.2%	-2.10 [-2.84, -1.36]
Mardani-Kivi 2016	4.9	1.09	37	5.4	1.04	34	4.5%	-0.50 [-1.00, -0.00]
Metry 2008	1.252	0.956	67	2.41	1.3	34	4.5%	-1.16 [-1.65, -0.66]
Montazeri 2007	5.73	1.93	35	7.05	1.81	35	4.1%	-1.32 [-2.20, -0.44]
Nesioonpour 2014	2.26	1.23	31	3.77	1.68	31	4.3%	-1.51 [-2.24, -0.78]
Pandey 2004 B	3.5	2.3	28	6.1	1.7	28	3.8%	-2.60 [-3.66, -1.54]
Pandey 2005	3.65	1.314	80	6.15	1.3	20	4.4%	-2.50 [-3.14, -1.86]
Pandey 2005 B	2.95	1.252	40	5	1	20	4.4%	-2.05 [-2.64, -1.46]
Said-Ahmed 2007	2.6	1.34	60	4.2	1.1	20	4.4%	-1.60 [-2.19, -1.01]
Tuncer 2005	1.9	2.266	30	2.4	1.7	15	3.6%	-0.50 [-1.68, 0.68]
Turan 2004 B	1.8	1.6	25	4.2	1	25	4.2%	-2.40 [-3.14, -1.66]
Vahedi 2011	6.111	2.094	36	5.675	2.443	40	3.9%	0.44 [-0.58, 1.46]
Total (95% CI)			**1000**			**706**	**100.0%**	**-1.46 [-1.91, -1.01]**

Heterogeneity: Tau² = 1.12; Chi² = 462.06, df = 22 (P < 0.00001); I² = 95%
Test for overall effect: Z = 6.31 (P < 0.00001)

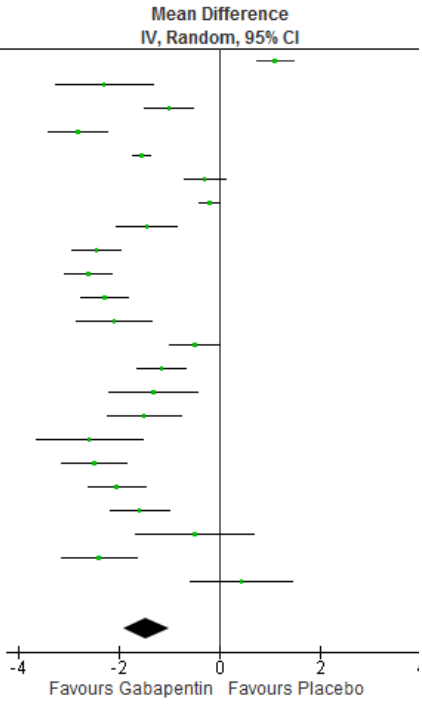


Figure 177: Pain score >6 - 24 hours

Study or Subgroup	Gabapentin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abdelmageed 2010	2.1	0.4	30	1	0.7	30	5.2%	1.10 [0.81, 1.39]
Ajori 2012	0.2	0.8	69	0.9	1.3	69	5.1%	-0.70 [-1.06, -0.34]
Al-Mujadi 2006	1.8	1.6	37	2.3	1.3	35	4.7%	-0.50 [-1.17, 0.17]
Behdad 2012	2.53	0.5	30	4.27	1.42	30	4.9%	-1.74 [-2.28, -1.20]
Ghafari 2009	1.81	0.3	33	3.48	0.4	33	5.3%	-1.67 [-1.84, -1.50]
Hanoura 2018	1.3	0.7	19	1.26	0.7	19	5.0%	0.04 [-0.41, 0.49]
Hosseini 2015	0.77	0.57	22	1.36	1.04	22	4.9%	-0.59 [-1.09, -0.09]
Khademi 2010	4.46	0.83	44	5.13	1.24	43	5.0%	-0.67 [-1.11, -0.23]
Khan 2011	2.983	0.997	150	3.5	0.8	25	5.1%	-0.52 [-0.87, -0.17]
Khan 2013	0.852	0.743	34	2.428	1.118	35	5.0%	-1.58 [-2.02, -1.13]
Marashi 2012	3.5	0.7	22	3.5	0.7	22	5.0%	0.00 [-0.41, 0.41]
Mardani-Kivi 2016	4.7	1.4	37	5.3	1.04	34	4.8%	-0.60 [-1.17, -0.03]
Metry 2008	1.849	1.506	67	2.3	1.3	34	4.8%	-0.45 [-1.02, 0.12]
Montazeri 2007	4.46	1.764	35	6.65	2.57	35	4.0%	-2.19 [-3.22, -1.16]
Nesioonpour 2014	4.68	2.02	31	6.58	2.51	31	3.8%	-1.90 [-3.03, -0.77]
Pandey 2004 B	1.2	1.3	28	2.1	1.2	28	4.7%	-0.90 [-1.56, -0.24]
Pandey 2005	2.575	1.53	80	4.5	1.4	20	4.6%	-1.92 [-2.62, -1.23]
Pandey 2005 B	2.55	1.8835	40	3.9	1	20	4.6%	-1.35 [-2.08, -0.62]
Said-Ahmed 2007	1.6	0.84	60	2.5	1.2	20	4.8%	-0.90 [-1.47, -0.33]
Turan 2004 B	0.5	0.7	25	1.6	1.2	25	4.9%	-1.10 [-1.64, -0.56]
Vahedi 2011	2.583	1.948	36	3.4	2.716	40	4.0%	-0.82 [-1.87, 0.24]
Total (95% CI)			**929**			**650**	**100.0%**	**-0.87 [-1.29, -0.46]**

Heterogeneity: Tau² = 0.85; Chi² = 347.45, df = 20 (P < 0.00001); I² = 94%
Test for overall effect: Z = 4.10 (P < 0.0001)

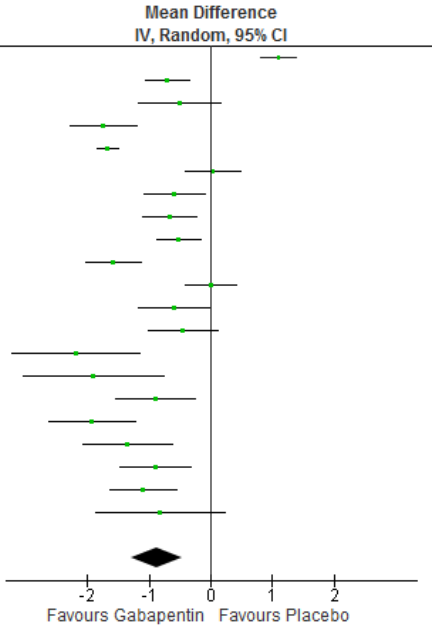


Figure 178: Dose of Opioid consumed ≤ 6 hours

Study or Subgroup	Gabapentin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Clarke 2013	8	19	22	25.7	36.3	22	10.5%	-0.60 [-1.21, 0.01]
Clarke 2013	0.8	2.1	22	1.3	2.8	22	10.6%	-0.20 [-0.79, 0.39]
Eidy 2017	27.8	3.5	36	30.6	1	36	11.7%	-1.08 [-1.57, -0.58]
Mardani-Kivi 2013	20	23.5	55	34	21	53	12.8%	-0.62 [-1.01, -0.24]
Mardani-Kivi 2016	20.5	13.34	37	40.3	9.82	34	11.1%	-1.66 [-2.21, -1.12]
Tuncer 2005	13.45	5.773	30	21.4	5.9	15	9.6%	-1.34 [-2.03, -0.66]
Turan 2004	2.4	1.8	25	6.4	4.3	25	10.5%	-1.19 [-1.80, -0.59]
Turan 2004 B	118.3	56.8	25	120.2	52	25	11.0%	-0.03 [-0.59, 0.52]
Vahedi 2011	5.333	3.207	36	6.4	3.455	40	12.1%	-0.32 [-0.77, 0.14]
Total (95% CI)			**288**			**272**	**100.0%**	**-0.77 [-1.12, -0.42]**

Heterogeneity: Tau² = 0.21; Chi² = 31.28, df = 8 (P = 0.0001); I² = 74%
Test for overall effect: Z = 4.30 (P < 0.0001)

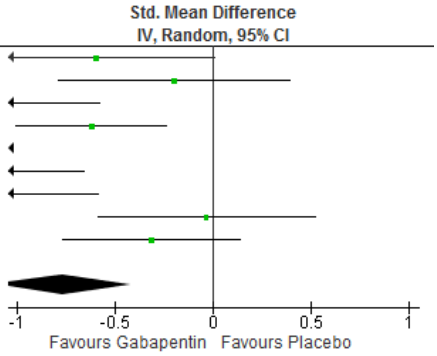


Figure 179: Dose of Opioid consumed >6 - 24 hours

Study or Subgroup	Gabapentin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abdelmageed 2010	48.8	9.7	30	93.8	8.4	30	2.9%	-4.90 [-5.93, -3.86]
Ajori 2012	1.4	0.6	69	2.5	0.7	69	3.5%	-1.68 [-2.07, -1.29]
Al-Mujadi 2006	15.2	7.6	37	29.5	9.9	35	3.4%	-1.61 [-2.14, -1.07]
Eidy 2017	79.9	1.8	36	89.2	2.8	36	3.2%	-3.91 [-4.71, -3.11]
Ghafari 2009	15.78	1.15	33	26.94	2.28	33	2.8%	-6.11 [-7.29, -4.93]
Hanoura 2018	27.1	5.1	19	31	5.1	19	3.3%	-0.75 [-1.41, -0.09]
Hassani 2015	20.7	13.7	30	32.5	14.1	30	3.4%	-0.84 [-1.37, -0.31]
Hosseini 2015	65.91	11.81	22	78.41	13.3	22	3.3%	-0.98 [-1.60, -0.35]
Khademi 2010	28.33	12.9	44	35.1	15.1	43	3.5%	-0.48 [-0.90, -0.05]
Khan 2011	20.8	5.776	150	31.5	9.6	25	3.5%	-1.65 [-2.11, -1.20]
Khan 2013	13.21	4.708	34	24.31	9.276	35	3.4%	-1.49 [-2.02, -0.95]
Marashi 2012	18.3	15.6	22	65.7	31.1	22	3.2%	-1.89 [-2.61, -1.17]
Mardani-Kivi 2013	25	23.84	55	37	25.26	53	3.5%	-0.49 [-0.87, -0.10]
Mardani-Kivi 2016	18.4	15.52	37	40	24.09	34	3.4%	-1.06 [-1.56, -0.56]
Metry 2008	16.09	7.788	67	29.2	9.6	34	3.5%	-1.54 [-2.01, -1.08]
Mohammad 2012	8	1	40	14	2	40	3.2%	-3.76 [-4.50, -3.02]
Montazeri 2007	15.43	2.54	35	17.94	3	35	3.4%	-0.89 [-1.39, -0.40]
Nesioonpour 2014	13.54	14.67	31	53.22	17.67	31	3.3%	-2.41 [-3.08, -1.75]
Pandey 2004 B	233.5	141.9	28	359.6	104.1	28	3.4%	-1.00 [-1.56, -0.44]
Pandey 2005	737.9	205.3	80	1,217.5	182	20	3.4%	-2.37 [-2.96, -1.77]
Pandey 2005 B	593.65	234.59	40	924.7	417.5	20	3.4%	-1.07 [-1.64, -0.49]
Pandey 2006	221.2	92.4	125	505.9	82	125	3.5%	-3.25 [-3.63, -2.87]
Radhakrishnan 2005	20.9	9.6	30	20.5	9.26	30	3.4%	0.04 [-0.46, 0.55]
Said-Ahmed 2007	263.37	91.64	60	340	95	20	3.4%	-0.82 [-1.34, -0.30]
Soltanzadeh 2011	2.5	0.9	30	4	1.5	30	3.4%	-1.20 [-1.75, -0.64]
Srivastava 2010	253.9	44.8	60	375.8	83.5	60	3.5%	-1.81 [-2.23, -1.38]
Syal 2010	106.33	32.07	30	203.83	41.5	30	3.3%	-2.59 [-3.29, -1.90]
Turan 2004	3.8	4.6	25	11.4	5.4	25	3.3%	-1.49 [-2.12, -0.86]
Turan 2004 B	10.1	5	25	28.2	4	25	3.0%	-3.93 [-4.91, -2.96]
Vahedi 2011	3.944	3.43	36	4.1	3.761	40	3.5%	-0.04 [-0.49, 0.41]
Total (95% CI)			**1360**			**1079**	**100.0%**	**-1.80 [-2.20, -1.40]**

Heterogeneity: Tau² = 1.14; Chi² = 465.48, df = 29 (P < 0.00001); I² = 94%
Test for overall effect: Z = 8.87 (P < 0.00001)

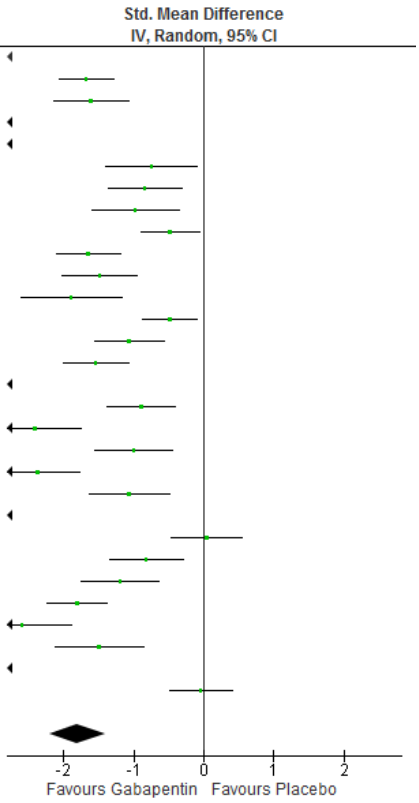


Figure 180: Respiratory Depression

Study or Subgroup	Gabapentin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pandey 2005	7	80	1	20	51.6%	1.75 [0.23, 13.42]
Srivastava 2010	0	60	1	60	48.4%	0.33 [0.01, 8.02]
Total (95% CI)		**140**		**80**	**100.0%**	**1.06 [0.21, 5.27]**
Total events	7		2			

Heterogeneity: Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)

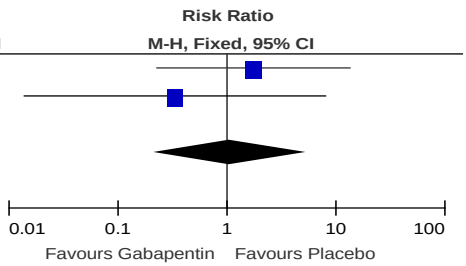


Figure 181: Nausea ≤ 6 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Behdad 2012	21	30	18	31	62.0%	1.21 [0.82, 1.76]
Dirks 2002	2	31	3	34	10.0%	0.73 [0.13, 4.09]
Tuncer 2005	12	30	6	15	28.0%	1.00 [0.47, 2.14]
Total (95% CI)		**91**		**80**	**100.0%**	**1.10 [0.78, 1.56]**
Total events	35		27			

Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)

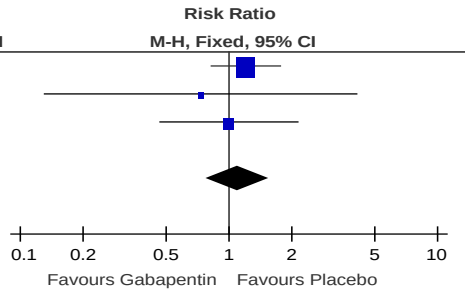


Figure 182: Nausea >6 - 24 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelmageed 2010	5	30	13	30	8.2%	0.38 [0.16, 0.94]
Ajori 2012	8	69	19	69	12.0%	0.42 [0.20, 0.90]
Behdad 2012	9	30	4	31	2.5%	2.33 [0.80, 6.75]
Dierking 2004	12	39	11	32	7.6%	0.90 [0.46, 1.75]
Durmus 2007	7	25	9	25	5.7%	0.78 [0.34, 1.76]
Eidy 2017	7	36	11	36	6.9%	0.64 [0.28, 1.46]
Ghafari 2009	5	33	7	33	4.4%	0.71 [0.25, 2.02]
Hanoura 2018	6	19	2	19	1.3%	3.00 [0.69, 13.03]
Khan 2011	12	150	2	25	2.2%	1.00 [0.24, 4.20]
Mohammad 2012	3	40	10	40	6.3%	0.30 [0.09, 1.01]
Mohammadi 2008	2	35	9	35	5.7%	0.22 [0.05, 0.96]
Montazeri 2007	6	35	5	35	3.2%	1.20 [0.40, 3.57]
Pandey 2004 B	5	28	4	28	2.5%	1.25 [0.37, 4.17]
Pandey 2005	5	80	1	20	1.0%	1.25 [0.15, 10.11]
Pandey 2005 B	6	40	3	20	2.5%	1.00 [0.28, 3.59]
Radhakrishnan 2005	6	30	6	30	3.8%	1.00 [0.36, 2.75]
Said-Ahmed 2007	12	60	5	20	4.7%	0.80 [0.32, 1.99]
Siddiqui 2014	17	36	17	36	10.7%	1.00 [0.61, 1.63]
Turan 2004	5	25	7	25	4.4%	0.71 [0.26, 1.95]
Turan 2004 B	5	25	7	25	4.4%	0.71 [0.26, 1.95]
Total (95% CI)		**865**		**614**	**100.0%**	**0.77 [0.63, 0.95]**
Total events	143		152			

Heterogeneity: Chi² = 20.83, df = 19 (P = 0.35); I² = 9%
Test for overall effect: Z = 2.46 (P = 0.01)

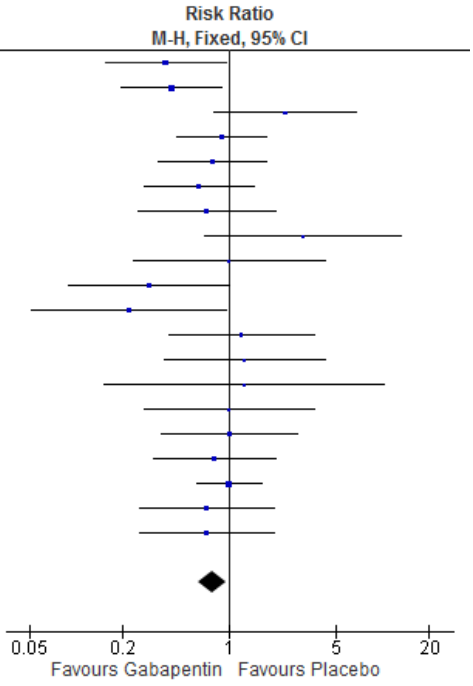


Figure 183: Vomiting ≤ 6 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Behdad 2012	20	30	20	30	88.2%	1.00 [0.70, 1.43]
Tuncer 2005	3	30	2	15	11.8%	0.75 [0.14, 4.02]
Total (95% CI)		**60**		**45**	**100.0%**	**0.97 [0.67, 1.40]**
Total events	23		22			

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)

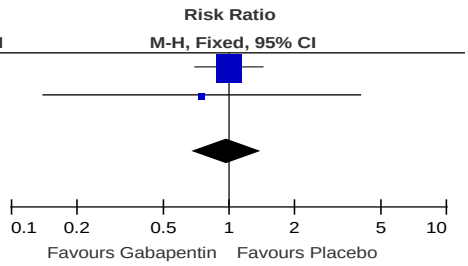


Figure 184: Vomiting >6 - 24 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelmageed 2010	2	30	9	30	5.9%	0.22 [0.05, 0.94]
Ajori 2012	5	69	16	69	10.6%	0.31 [0.12, 0.81]
Behdad 2012	15	30	13	30	8.6%	1.15 [0.67, 1.99]
Dierking 2004	18	39	15	32	10.9%	0.98 [0.60, 1.62]
Durmus 2007	3	25	6	25	4.0%	0.50 [0.14, 1.78]
Eidy 2017	16	36	24	36	15.9%	0.67 [0.43, 1.03]
Ghafari 2009	4	33	9	33	5.9%	0.44 [0.15, 1.30]
Hanoura 2018	3	19	1	19	0.7%	3.00 [0.34, 26.33]
Khan 2011	8	150	1	25	1.1%	1.33 [0.17, 10.21]
Metry 2008	2	67	1	34	0.9%	1.01 [0.10, 10.80]
Mohammad 2012	1	40	5	40	3.3%	0.20 [0.02, 1.64]
Mohammadi 2008	0	35	4	35	3.0%	0.11 [0.01, 1.99]
Montazeri 2007	4	35	3	35	2.0%	1.33 [0.32, 5.53]
Pandey 2004 B	3	28	4	28	2.6%	0.75 [0.18, 3.05]
Pandey 2005	7	80	2	20	2.1%	0.88 [0.20, 3.89]
Pandey 2005 B	2	40	2	20	1.8%	0.50 [0.08, 3.29]
Radhakrishnan 2005	2	30	3	30	2.0%	0.67 [0.12, 3.71]
Said-Ahmed 2007	10	60	5	20	5.0%	0.67 [0.26, 1.72]
Siddiqui 2014	5	36	6	36	4.0%	0.83 [0.28, 2.49]
Turan 2004	1	25	6	25	4.0%	0.17 [0.02, 1.29]
Turan 2004 B	6	25	9	25	5.9%	0.67 [0.28, 1.59]
Total (95% CI)		**932**		**647**	**100.0%**	**0.66 [0.53, 0.81]**
Total events	117		144			

Heterogeneity: Chi² = 20.12, df = 20 (P = 0.45); I² = 1%
Test for overall effect: Z = 3.84 (P = 0.0001)

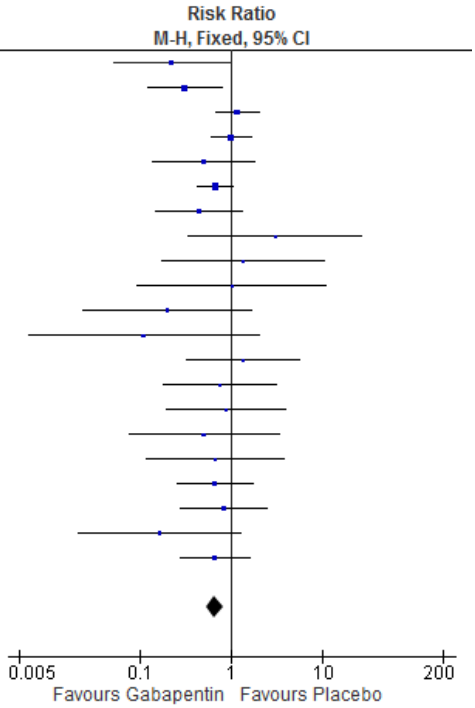


Figure 185: Nausea & Vomiting ≤ 6 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mardani-Kivi 2013	5	55	7	53	38.3%	0.69 [0.23, 2.03]
Mardani-Kivi 2016	1	37	11	34	61.7%	0.08 [0.01, 0.61]
Total (95% CI)		**92**		**87**	**100.0%**	**0.32 [0.13, 0.76]**
Total events	6		18			

Heterogeneity: Chi² = 3.70, df = 1 (P = 0.05); I² = 73%
Test for overall effect: Z = 2.57 (P = 0.01)

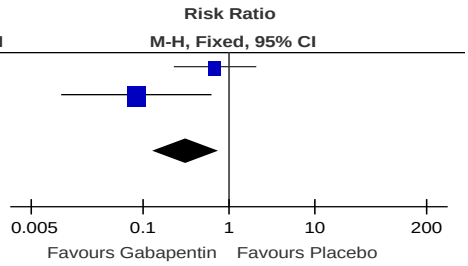


Figure 186: Nausea & Vomiting

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hassani 2015	3	30	10	30	9.5%	0.30 [0.09, 0.98]
Khademi 2010	16	44	28	43	19.4%	0.56 [0.36, 0.87]
Mardani-Kivi 2013	3	55	4	53	7.4%	0.72 [0.17, 3.08]
Mardani-Kivi 2016	1	37	2	34	3.5%	0.46 [0.04, 4.84]
Pandey 2006	46	125	75	125	21.8%	0.61 [0.47, 0.80]
Srivastava 2010	15	60	31	60	18.6%	0.48 [0.29, 0.80]
Syal 2010	25	30	14	30	19.9%	1.79 [1.18, 2.70]
Total (95% CI)		**381**		**375**	**100.0%**	**0.67 [0.42, 1.07]**
Total events	109		164			

Heterogeneity: Tau² = 0.25; Chi² = 26.20, df = 6 (P = 0.0002); I² = 77%
Test for overall effect: Z = 1.67 (P = 0.09)

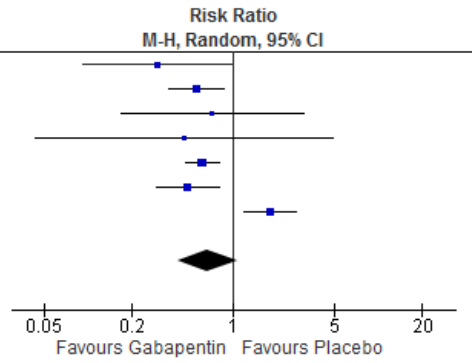


Figure 187: Dizziness ≤ 6 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Behdad 2012	4	30	1	31	3.0%	4.13 [0.49, 34.89]
Dirks 2002	8	31	11	34	31.6%	0.80 [0.37, 1.72]
Mardani-Kivi 2013	7	55	4	53	12.3%	1.69 [0.52, 5.43]
Mardani-Kivi 2016	6	37	8	34	25.1%	0.69 [0.27, 1.78]
Tuncer 2005	14	30	7	15	28.1%	1.00 [0.52, 1.94]
Total (95% CI)		**183**		**167**	**100.0%**	**1.04 [0.69, 1.56]**
Total events	39		31			

Heterogeneity: Chi² = 3.44, df = 4 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)

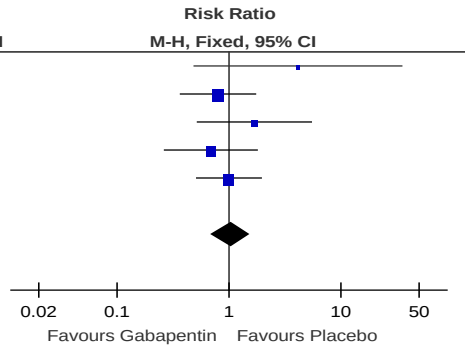


Figure 188: Dizziness >6 - 24 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelmageed 2010	6	30	5	30	9.2%	1.20 [0.41, 3.51]
Behdad 2012	5	30	0	31	0.9%	11.35 [0.66, 196.81]
Dierking 2004	23	39	15	32	30.2%	1.26 [0.80, 1.98]
Ghafari 2009	2	33	2	33	3.7%	1.00 [0.15, 6.68]
Hanoura 2018	4	19	0	19	0.9%	9.00 [0.52, 156.41]
Khan 2011	5	150	1	25	3.1%	0.83 [0.10, 6.84]
Mardani-Kivi 2013	3	55	6	53	11.2%	0.48 [0.13, 1.83]
Mardani-Kivi 2016	5	37	3	34	5.7%	1.53 [0.40, 5.93]
Montazeri 2007	1	35	0	35	0.9%	3.00 [0.13, 71.22]
Pandey 2004 B	1	28	0	28	0.9%	3.00 [0.13, 70.64]
Said-Ahmed 2007	12	60	3	20	8.3%	1.33 [0.42, 4.25]
Srivastava 2010	5	60	7	60	12.8%	0.71 [0.24, 2.13]
Turan 2004	6	25	4	25	7.3%	1.50 [0.48, 4.68]
Turan 2004 B	2	25	1	25	1.8%	2.00 [0.19, 20.67]
Waikakul 2011	0	26	1	24	2.9%	0.31 [0.01, 7.23]
Total (95% CI)		**652**		**474**	**100.0%**	**1.29 [0.95, 1.77]**
Total events	80		48			

Heterogeneity: Chi² = 9.12, df = 14 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.62 (P = 0.11)

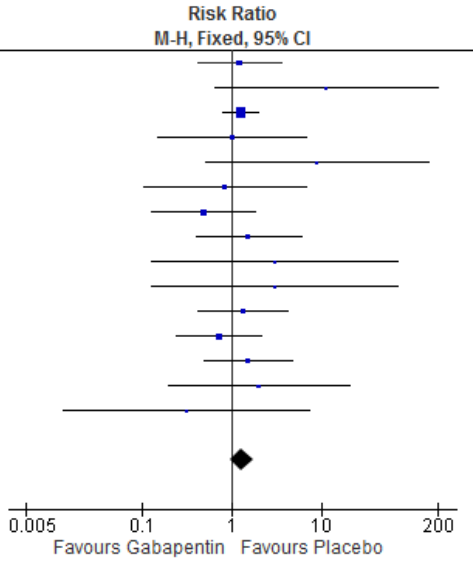


Figure 189: Somnolence ≤ 6 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dirks 2002	20	31	22	34	100.0%	1.00 [0.70, 1.43]
Total (95% CI)		**31**		**34**	**100.0%**	**1.00 [0.70, 1.43]**
Total events	20		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.99)

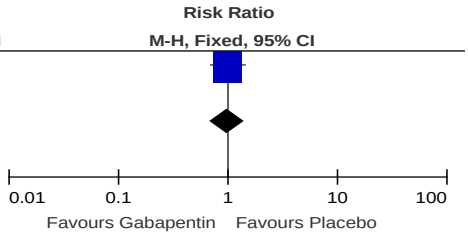


Figure 190: Somnolence >6 - 24 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelmageed 2010	2	30	1	30	6.4%	2.00 [0.19, 20.90]
Ghafari 2009	2	33	3	33	19.3%	0.67 [0.12, 3.73]
Hanoura 2018	4	19	0	19	3.2%	9.00 [0.52, 156.41]
Khan 2011	8	150	1	25	11.0%	1.33 [0.17, 10.21]
Pandey 2005 B	3	40	1	20	8.6%	1.50 [0.17, 13.52]
Pandey 2006	4	125	2	125	12.8%	2.00 [0.37, 10.72]
Radhakrishnan 2005	1	30	1	30	6.4%	1.00 [0.07, 15.26]
Said-Ahmed 2007	8	60	2	20	19.3%	1.33 [0.31, 5.77]
Siddiqui 2014	28	36	38	36		Not estimable
Turan 2004	2	25	1	25	6.4%	2.00 [0.19, 20.67]
Turan 2004 B	1	25	0	25	3.2%	3.00 [0.13, 70.30]
Waikakul 2011	1	26	0	24	3.3%	2.78 [0.12, 65.08]
Total (95% CI)		**599**		**412**	**100.0%**	**1.72 [0.93, 3.18]**
Total events	64		50			

Heterogeneity: Chi² = 3.06, df = 10 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)

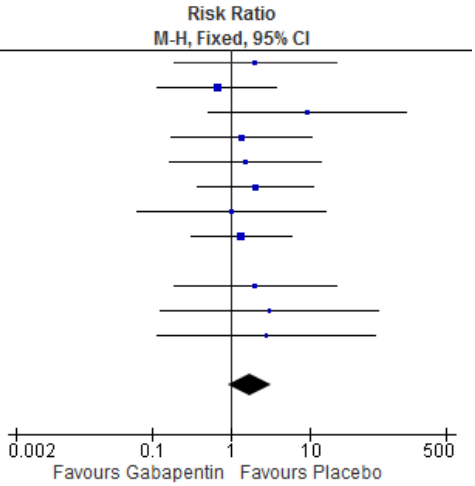


Figure 191: Sedation ≤ 6 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mardani-Kivi 2013	6	55	3	53	42.3%	1.93 [0.51, 7.31]
Mardani-Kivi 2016	5	37	4	34	57.7%	1.15 [0.34, 3.93]
Total (95% CI)		**92**		**87**	**100.0%**	**1.48 [0.60, 3.63]**
Total events	11		7			

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.39)

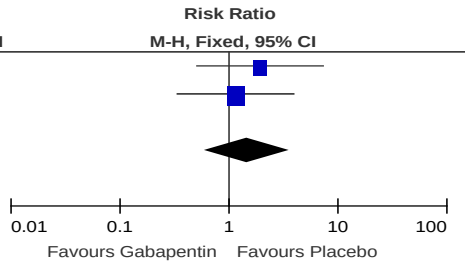


Figure 192: Sedation

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelmageed 2010	6	30	5	30	10.5%	1.20 [0.41, 3.51]
Mardani-Kivi 2013	2	55	3	53	6.4%	0.64 [0.11, 3.69]
Mardani-Kivi 2016	3	37	2	34	4.4%	1.38 [0.24, 7.76]
Srivastava 2010	14	60	8	60	16.8%	1.75 [0.79, 3.86]
Syal 2010	30	30	29	30	61.9%	1.03 [0.94, 1.13]
Total (95% CI)		**212**		**207**	**100.0%**	**1.16 [0.92, 1.47]**
Total events	55		47			

Heterogeneity: Chi² = 7.76, df = 4 (P = 0.10); I² = 48%
Test for overall effect: Z = 1.24 (P = 0.22)

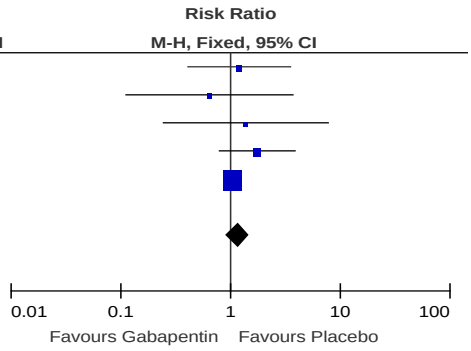


Figure 193: Urinary Retention

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Al-Mujadi 2006	1	37	0	35	2.7%	2.84 [0.12, 67.53]
Mohammad 2012	0	40	1	40	7.9%	0.33 [0.01, 7.95]
Radhakrishnan 2005	8	30	7	30	36.8%	1.14 [0.47, 2.75]
Siddiqui 2014	2	36	1	36	5.3%	2.00 [0.19, 21.09]
Turan 2004	0	25	5	25	28.9%	0.09 [0.01, 1.56]
Turan 2004 B	1	25	3	25	15.8%	0.33 [0.04, 2.99]
Waikakul 2011	1	26	0	24	2.7%	2.78 [0.12, 65.08]
Total (95% CI)		**219**		**215**	**100.0%**	**0.78 [0.42, 1.47]**
Total events	13		17			

Heterogeneity: Chi² = 5.64, df = 6 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)

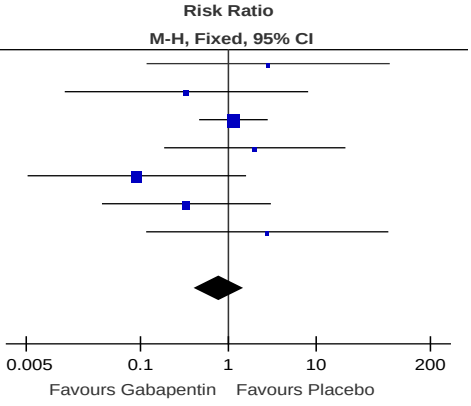


Figure 194: Dry Mouth

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Radhakrishnan 2005	1	30	0	30	100.0%	7.39 [0.15, 372.38]
Siddiqui 2014	36	36	36	36		Not estimable
Total (95% CI)		**66**		**66**	**100.0%**	**7.39 [0.15, 372.38]**
Total events	37		36			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

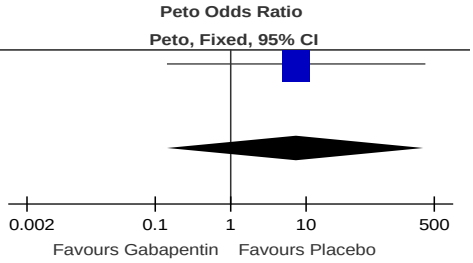


Figure 195: Pruritus

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Durmus 2007	1	25	2	25	6.0%	0.50 [0.05, 5.03]
Ghafari 2009	2	33	4	33	11.6%	0.49 [0.09, 2.57]
Pandey 2005 B	2	40	2	20	7.1%	0.45 [0.05, 3.83]
Pandey 2006	1	125	3	125	8.3%	0.36 [0.05, 2.61]
Radhakrishnan 2005	0	30	2	30	4.1%	0.13 [0.01, 2.14]
Siddiqui 2014	24	36	23	36	34.7%	1.13 [0.43, 2.96]
Srivastava 2010	4	60	3	60	13.9%	1.35 [0.30, 6.18]
Turan 2004	1	25	2	25	6.0%	0.50 [0.05, 5.03]
Turan 2004 B	0	25	2	25	4.1%	0.13 [0.01, 2.14]
Waikakul 2011	0	26	2	24	4.1%	0.12 [0.01, 1.97]
Total (95% CI)		**425**		**403**	**100.0%**	**0.62 [0.35, 1.09]**
Total events	35		45			

Heterogeneity: Chi² = 6.72, df = 9 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)

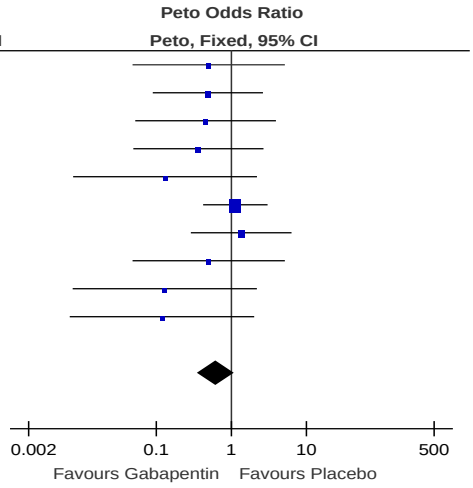


Figure 196: Headache ≤ 6 hours

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dirks 2002	1	31	1	34	15.2%	1.10 [0.07, 16.80]
Tuncer 2005	7	30	4	15	84.8%	0.88 [0.30, 2.53]
Total (95% CI)		**61**		**49**	**100.0%**	**0.91 [0.34, 2.45]**
Total events	8		5			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)

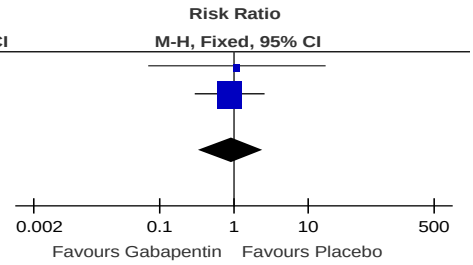


Figure 197: Headache

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Durmus 2007	1	25	1	25	9.0%	1.00 [0.06, 16.45]
Hassani 2015	1	30	3	30	17.5%	0.35 [0.05, 2.61]
Pandey 2005 B	1	40	0	20	4.1%	4.48 [0.07, 286.49]
Pandey 2006	2	125	0	125	9.2%	7.45 [0.46, 119.76]
Radhakrishnan 2005	0	30	3	30	13.4%	0.13 [0.01, 1.26]
Siddiqui 2014	5	36	7	36	46.8%	0.67 [0.20, 2.31]
Total (95% CI)		**286**		**266**	**100.0%**	**0.67 [0.29, 1.56]**
Total events	10		14			

Heterogeneity: Chi² = 6.20, df = 5 (P = 0.29); I² = 19%
Test for overall effect: Z = 0.93 (P = 0.35)

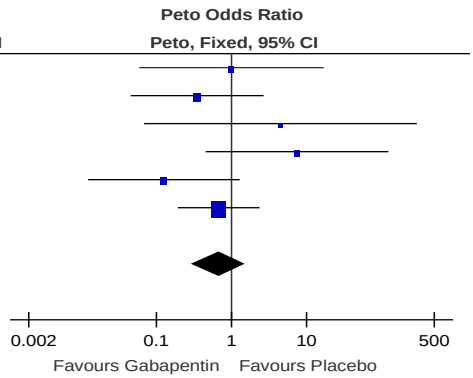


Figure 198: Light headed

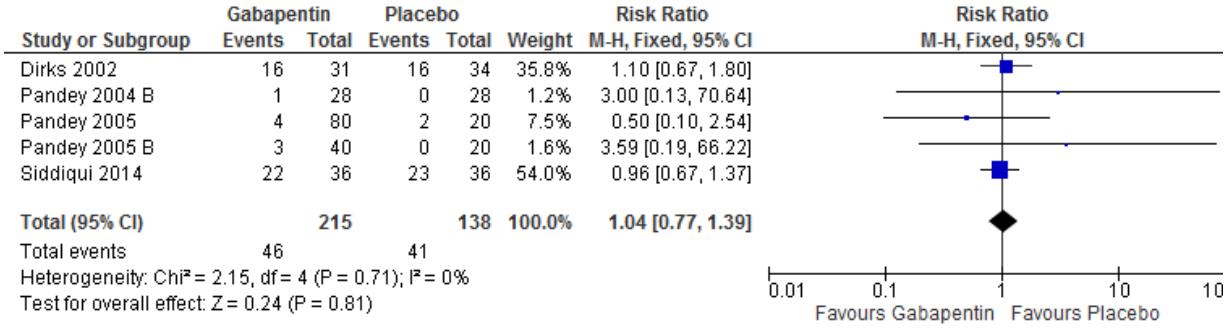
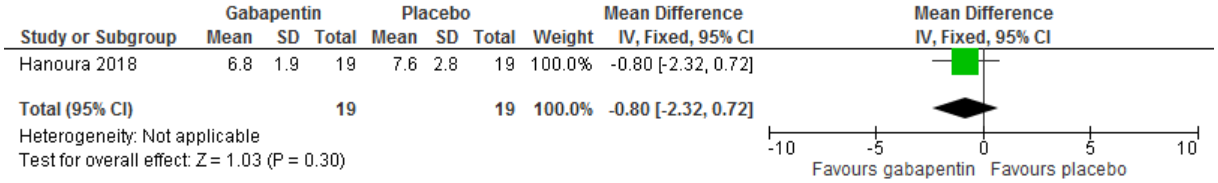


Figure 199: Length of stay



D.2 Pregabalin vs Placebo for managing acute post-operative pain

Figure 200: Pain score ≤ 6 hours

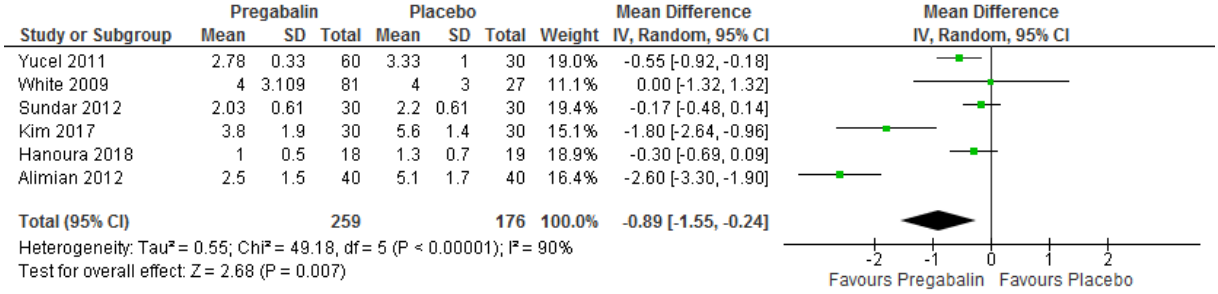


Figure 201: Pain score >6 - 24 hours

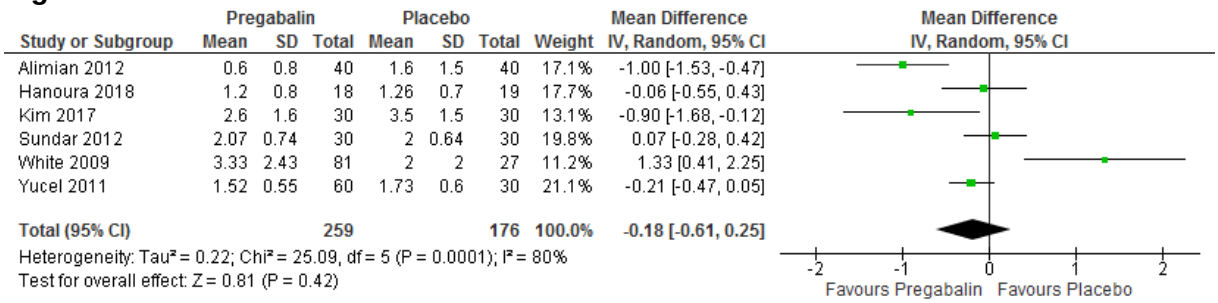


Figure 202: Dose of Opioid consumed ≤ 6 hours

Study or Subgroup	Pregabalin Mean	Pregabalin SD	Pregabalin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Balaban 2012	1.25	5.534	60	0	0	30		Not estimable
Eidy 2017	23.7	3.6	36	30.6	1	36	16.3%	-2.58 [-3.22, -1.95]
Eman 2014	6.9	2.5	20	8.9	1.4	20	16.2%	-0.97 [-1.63, -0.31]
Kim 2017	17	3	30	20	4	30	16.7%	-0.84 [-1.37, -0.31]
White 2009	85.67	107.1	81	93	76	27	17.1%	-0.07 [-0.51, 0.36]
Yucel 2011	25.19	4.47	60	32.6	5.3	30	16.9%	-1.54 [-2.04, -1.05]
Ziyaeifard 2015	5	0.2	30	4.9	0.2	30	16.8%	0.49 [-0.02, 1.01]
Total (95% CI)			**317**			**203**	**100.0%**	**-0.91 [-1.75, -0.07]**

Heterogeneity: Tau² = 1.02; Chi² = 74.26, df = 5 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.12 (P = 0.03)

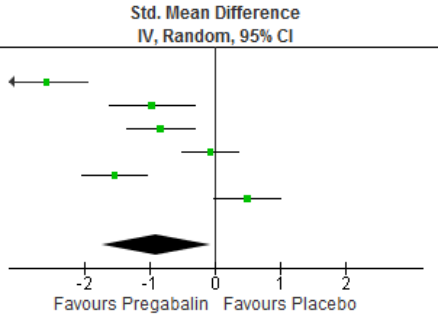


Figure 203: Dose of Opioid consumed >6 - 24 hours

Study or Subgroup	Pregabalin Mean	Pregabalin SD	Pregabalin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Eidy 2017	78.2	3.5	36	89.2	2.8	36	13.8%	-3.43 [-4.17, -2.69]
Eman 2014	19.9	6.5	20	35.1	5.5	20	13.3%	-2.47 [-3.32, -1.63]
Hanoura 2018	22.4	6	18	31	5.1	19	13.8%	-1.51 [-2.26, -0.77]
Kim 2017	40	5	30	44	4	30	14.7%	-0.87 [-1.40, -0.34]
Sundar 2012	241.67	178.87	30	251.67	181.47	30	14.8%	-0.05 [-0.56, 0.45]
Yucel 2011	37.3	5.9	60	46.97	6.67	30	14.8%	-1.56 [-2.05, -1.06]
Ziyaeifard 2015	3	0.17	30	3.1	0.15	30	14.7%	-0.62 [-1.13, -0.10]
Total (95% CI)			**224**			**195**	**100.0%**	**-1.47 [-2.26, -0.69]**

Heterogeneity: Tau² = 1.02; Chi² = 72.54, df = 6 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.67 (P = 0.0002)

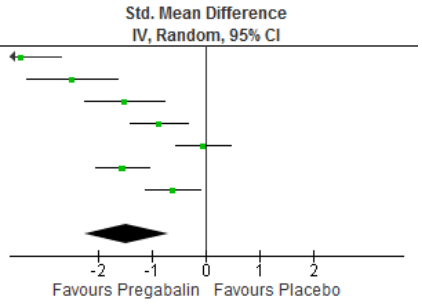


Figure 204: Nausea ≤ 6 hours

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2017	7	30	7	30	100.0%	1.00 [0.40, 2.50]
Total (95% CI)		**30**		**30**	**100.0%**	**1.00 [0.40, 2.50]**
Total events	7		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

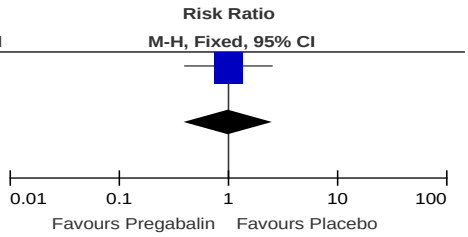


Figure 205: Nausea >6 - 24 hours

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alimian 2012	5	40	17	40	28.8%	0.29 [0.12, 0.72]
Balaban 2012	6	60	5	30	11.3%	0.60 [0.20, 1.81]
Eidy 2017	10	36	11	36	18.6%	0.91 [0.44, 1.87]
Eman 2014	3	20	4	20	6.8%	0.75 [0.19, 2.93]
Hanoura 2018	4	18	2	19	3.3%	2.11 [0.44, 10.15]
Kim 2017	3	30	5	30	8.5%	0.60 [0.16, 2.29]
Spreng 2011	7	22	14	24	22.7%	0.55 [0.27, 1.10]
Total (95% CI)		**226**		**199**	**100.0%**	**0.62 [0.43, 0.88]**
Total events	38		58			

Heterogeneity: Chi² = 6.30, df = 6 (P = 0.39); I² = 5%
Test for overall effect: Z = 2.65 (P = 0.008)

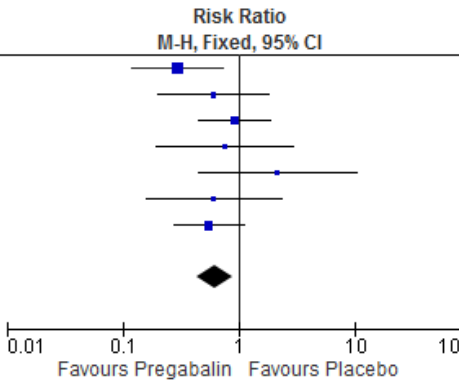


Figure 206: Vomiting >6 - 24 hours

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alimian 2012	1	40	5	40	11.6%	0.20 [0.02, 1.64]
Balaban 2012	6	60	9	30	28.0%	0.33 [0.13, 0.85]
Eidy 2017	13	36	24	36	55.9%	0.54 [0.33, 0.89]
Hanoura 2018	2	18	1	19	2.3%	2.11 [0.21, 21.32]
Spreng 2011	2	22	1	24	2.2%	2.18 [0.21, 22.42]
Sundar 2012	0	30	0	30		Not estimable
Total (95% CI)		**206**		**179**	**100.0%**	**0.52 [0.34, 0.78]**
Total events	24		40			

Heterogeneity: Chi² = 4.55, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 3.15 (P = 0.002)

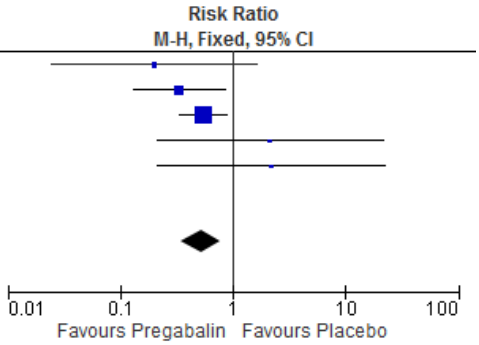


Figure 207: Nausea & Vomiting

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Agarwal 2008	14	27	15	29	67.4%	1.00 [0.60, 1.66]
Yucel 2011	7	60	7	60	32.6%	1.00 [0.37, 2.68]
Total (95% CI)		**87**		**89**	**100.0%**	**1.00 [0.63, 1.60]**
Total events	21		22			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)

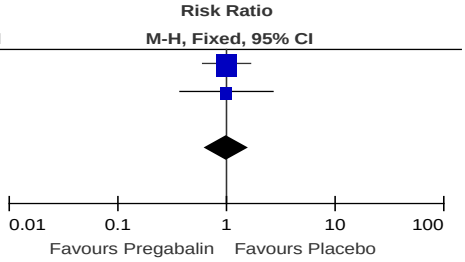


Figure 208: Sedation ≤ 6 hours

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kim 2017	1	30	0	30	100.0%	7.39 [0.15, 372.38]
Total (95% CI)		**30**		**30**	**100.0%**	**7.39 [0.15, 372.38]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

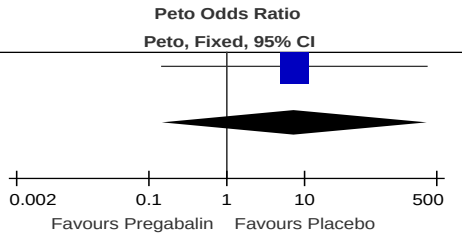


Figure 209: Sedation >6 - 24 hours

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kim 2017	0	30	0	30		Not estimable
Spreng 2011	3	22	2	24	100.0%	1.71 [0.27, 10.74]
Total (95% CI)		**52**		**54**	**100.0%**	**1.71 [0.27, 10.74]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

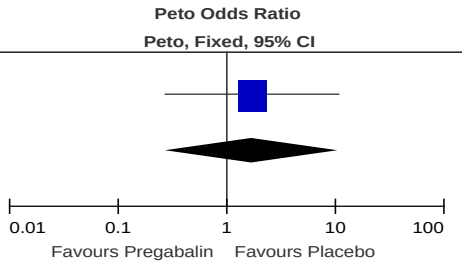


Figure 210: Ramsay Sedation Score ≤ 6 hours

Study or Subgroup	Pregabalin Mean	Pregabalin SD	Pregabalin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Balaban 2012	2	0	60	2	0	30		Not estimable
Yucel 2011	1.59	0.57	60	1.27	0.45	30	100.0%	0.32 [0.10, 0.54]
Total (95% CI)			**120**			**60**	**100.0%**	**0.32 [0.10, 0.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.90 (P = 0.004)

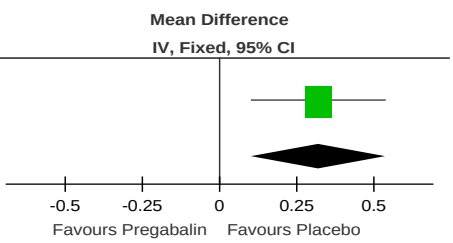


Figure 211: Ramsay Sedation Score >6 - 24 hours

Study or Subgroup	Pregabalin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Yucel 2011	1.17	0.42	60	1.1	0.31	30	100.0%	0.07 [-0.08, 0.22]
Total (95% CI)			**60**			**30**	**100.0%**	**0.07 [-0.08, 0.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

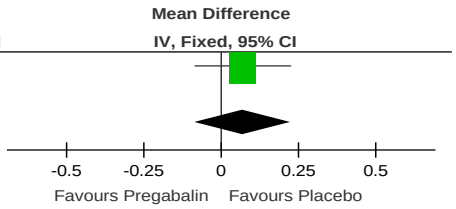


Figure 212: Dizziness ≤ 6 hours

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2017	2	30	2	30	57.1%	1.00 [0.15, 6.64]
White 2009	17	81	1	27	42.9%	5.67 [0.79, 40.60]
Total (95% CI)		**111**		**57**	**100.0%**	**3.00 [0.80, 11.20]**
Total events	19		3			

Heterogeneity: Chi² = 1.69, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.63 (P = 0.10)

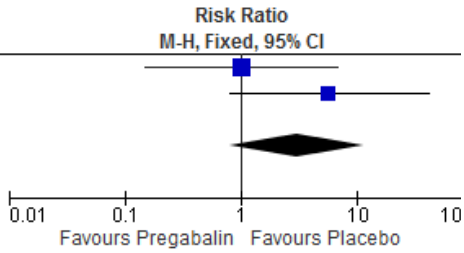


Figure 213: Dizziness 6 – 24 hours

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hanoura 2018	4	18	0	19	2.6%	9.47 [0.55, 164.35]
Kim 2017	1	30	3	30	15.8%	0.33 [0.04, 3.03]
Spreng 2011	2	22	5	24	25.3%	0.44 [0.09, 2.02]
Sundar 2012	0	30	0	30		Not estimable
Yucel 2011	21	60	8	30	56.3%	1.31 [0.66, 2.61]
Total (95% CI)		**160**		**133**	**100.0%**	**1.15 [0.66, 2.00]**
Total events	28		16			

Heterogeneity: Chi² = 4.98, df = 3 (P = 0.17); I² = 40%
Test for overall effect: Z = 0.48 (P = 0.63)

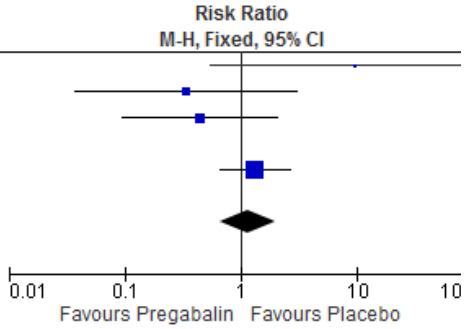


Figure 214: Pruritus

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balaban 2012	1	60	3	30	20.8%	0.17 [0.02, 1.54]
Eman 2014	1	20	0	20	2.6%	3.00 [0.13, 69.52]
Spreng 2011	1	22	7	24	34.9%	0.16 [0.02, 1.17]
Yucel 2011	10	60	6	30	41.7%	0.83 [0.33, 2.08]
Total (95% CI)		**162**		**104**	**100.0%**	**0.51 [0.26, 1.04]**
Total events	13		16			

Heterogeneity: Chi² = 4.62, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 1.86 (P = 0.06)

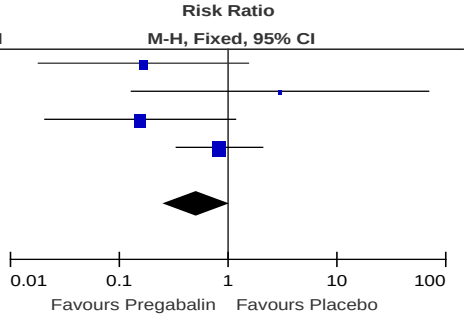


Figure 215: Urinary Retention

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balaban 2012	0	60	1	30	29.4%	0.17 [0.01, 4.04]
Spreng 2011	5	22	5	24	70.6%	1.09 [0.36, 3.27]
Total (95% CI)		**82**		**54**	**100.0%**	**0.82 [0.31, 2.20]**
Total events	5		6			

Heterogeneity: Chi² = 1.21, df = 1 (P = 0.27); I² = 17%
Test for overall effect: Z = 0.39 (P = 0.69)

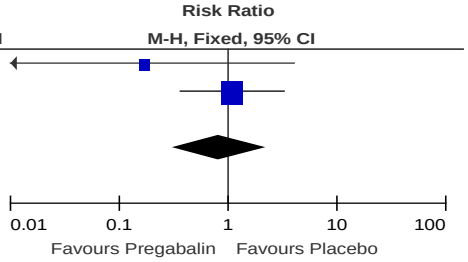


Figure 216: Respiratory Depression

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Agarwal 2008	1	27	0	29	50.2%	3.21 [0.14, 75.68]
Spreng 2011	2	22	0	24	49.8%	5.43 [0.28, 107.33]
Total (95% CI)		**49**		**53**	**100.0%**	**4.32 [0.50, 37.31]**
Total events	3		0			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)

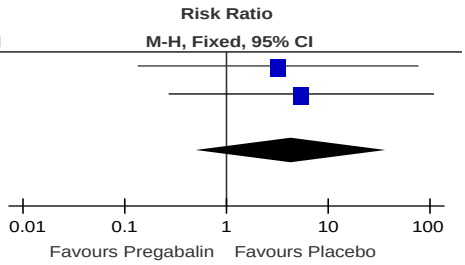


Figure 217: Headache ≤ 6 hours

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2017	5	30	4	30	100.0%	1.25 [0.37, 4.21]
Total (95% CI)		**30**		**30**	**100.0%**	**1.25 [0.37, 4.21]**
Total events	5		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

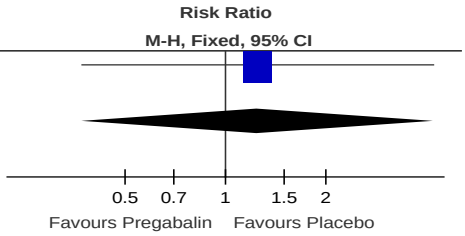


Figure 218: Headache >6 - 24 hours

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Agarwal 2008	8	27	6	29	49.5%	1.43 [0.57, 3.59]
Kim 2017	3	30	4	30	34.2%	0.75 [0.18, 3.07]
Spreng 2011	2	22	2	24	16.4%	1.09 [0.17, 7.10]
Total (95% CI)		**79**		**83**	**100.0%**	**1.14 [0.56, 2.32]**
Total events	13		12			

Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

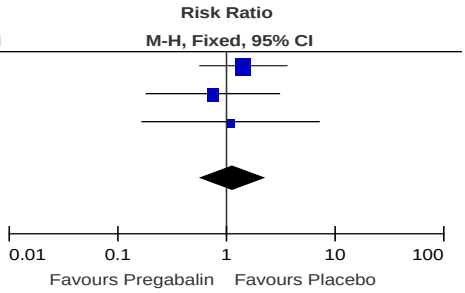


Figure 219: Somnolence

Study or Subgroup	Pregabalin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balaban 2012	0	60	1	30	80.3%	0.17 [0.01, 4.04]
Hanoura 2018	4	18	0	19	19.7%	9.47 [0.55, 164.35]
Total (95% CI)		**78**		**49**	**100.0%**	**2.00 [0.48, 8.35]**
Total events	4		1			

Heterogeneity: Chi² = 3.47, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.95 (P = 0.34)

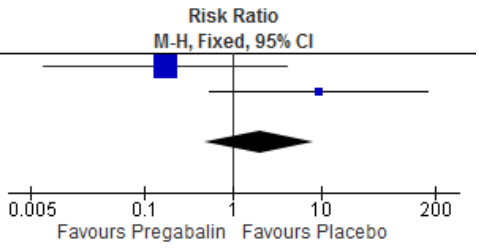
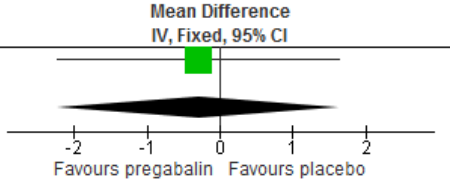


Figure 220: Length of stay

Study or Subgroup	Pregabalin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hanoura 2018	7.3	3.2	18	7.6	2.8	19	100.0%	-0.30 [-2.24, 1.64]
Total (95% CI)			**18**			**19**	**100.0%**	**-0.30 [-2.24, 1.64]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)



D.3 Gabapentin vs Pregabalin for managing acute post-operative pain

Figure 221: Pain score ≤ 6 hours

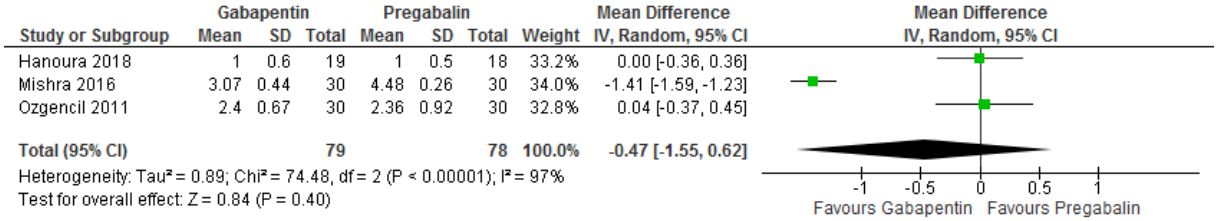


Figure 222: Pain score >6 - 24 hours

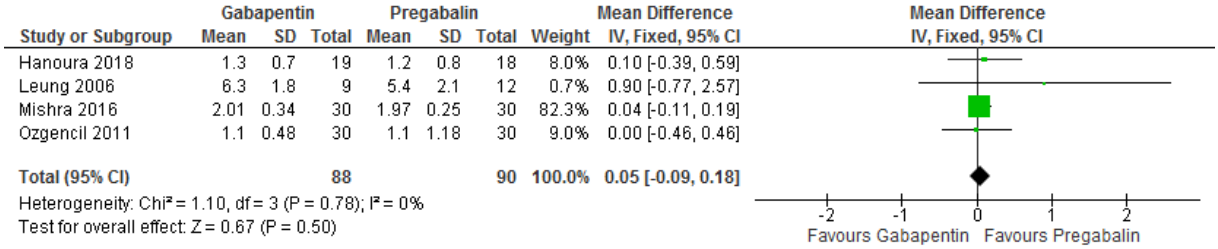


Figure 223: Dose of Opioid consumed <6 hours

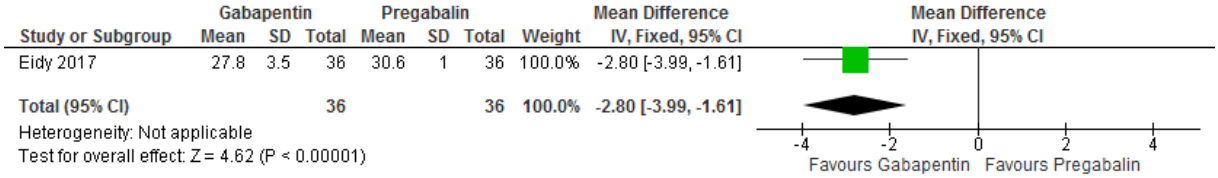


Figure 224: Dose of Opioid consumed >6 – 24 hours

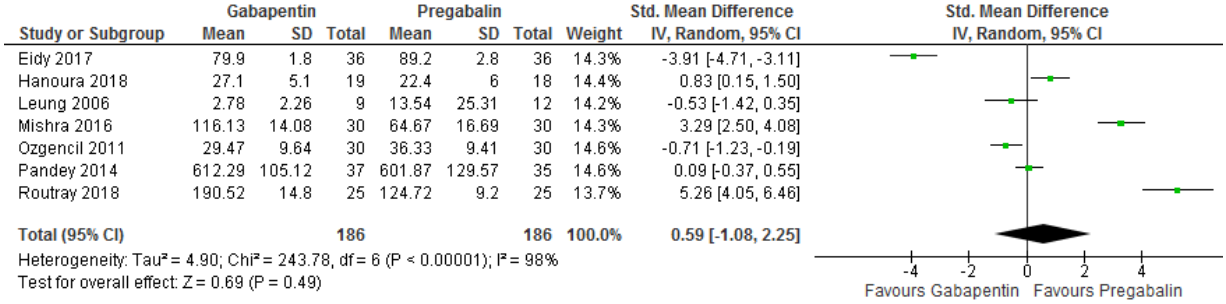


Figure 225: Sedation

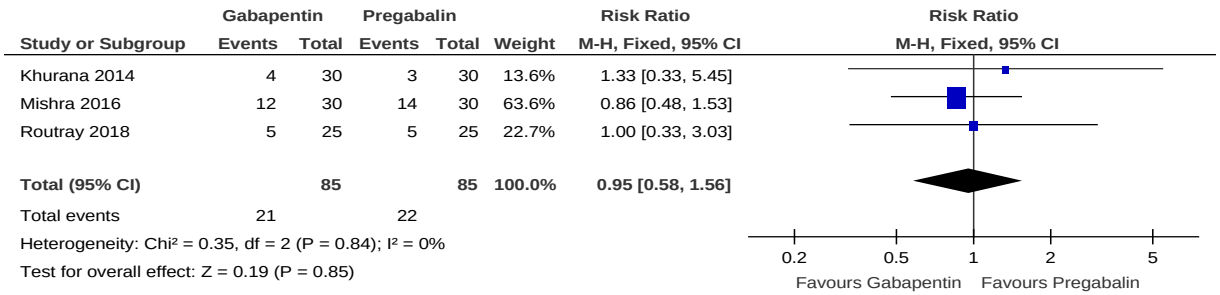


Figure 226: Respiratory Depression

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mishra 2016	2	30	3	30	100.0%	0.67 [0.12, 3.71]
Total (95% CI)		**30**		**30**	**100.0%**	**0.67 [0.12, 3.71]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)

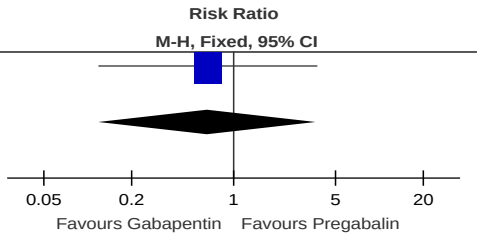


Figure 227: Nausea

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eidy 2017	7	36	10	36	39.8%	0.70 [0.30, 1.63]
Hanoura 2018	6	19	4	18	16.4%	1.42 [0.48, 4.22]
Khurana 2014	2	30	4	30	15.9%	0.50 [0.10, 2.53]
Ozgencil 2011	8	30	5	30	19.9%	1.60 [0.59, 4.33]
Routray 2018	3	25	2	25	8.0%	1.50 [0.27, 8.22]
Total (95% CI)		**140**		**139**	**100.0%**	**1.03 [0.63, 1.68]**
Total events	26		25			

Heterogeneity: Chi² = 2.84, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)

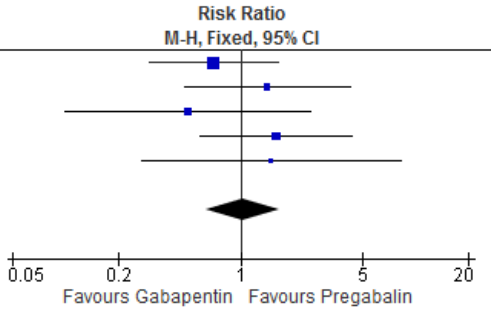


Figure 228: Vomiting

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eidy 2017	16	36	13	36	57.6%	1.23 [0.70, 2.17]
Hanoura 2018	3	19	2	18	9.1%	1.42 [0.27, 7.54]
Khurana 2014	1	30	0	30	2.2%	3.00 [0.13, 70.83]
Ozgencil 2011	3	30	3	30	13.3%	1.00 [0.22, 4.56]
Routray 2018	4	25	4	25	17.7%	1.00 [0.28, 3.56]
Total (95% CI)		**140**		**139**	**100.0%**	**1.22 [0.76, 1.95]**
Total events	27		22			

Heterogeneity: Chi² = 0.50, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)

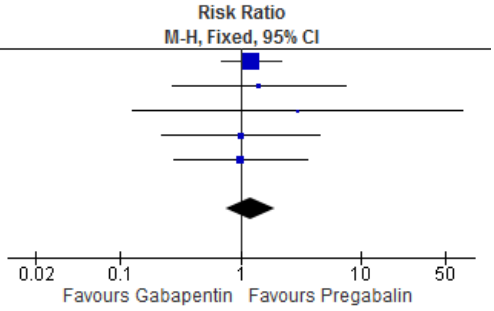


Figure 229: Nausea & Vomiting

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mishra 2016	5	30	4	30	100.0%	1.25 [0.37, 4.21]
Total (95% CI)		**30**		**30**	**100.0%**	**1.25 [0.37, 4.21]**
Total events	5		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

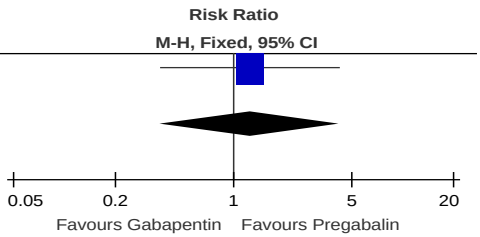


Figure 230: Dizziness

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hanoura 2018	4	19	3	18	20.4%	1.26 [0.33, 4.88]
Ozgencil 2011	9	30	8	30	53.0%	1.13 [0.50, 2.52]
Routray 2018	5	25	4	25	26.5%	1.25 [0.38, 4.12]
Total (95% CI)		**74**		**73**	**100.0%**	**1.19 [0.65, 2.16]**
Total events	18		15			

Heterogeneity: Chi² = 0.03, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)

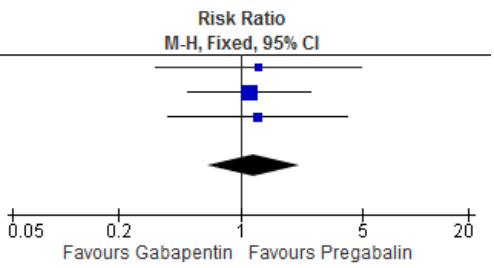


Figure 231: Somnolence

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hanoura 2018	4	19	4	18	37.0%	0.95 [0.28, 3.23]
Ozgencil 2011	8	30	7	30	63.0%	1.14 [0.47, 2.75]
Total (95% CI)		**49**		**48**	**100.0%**	**1.07 [0.52, 2.19]**
Total events	12		11			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)

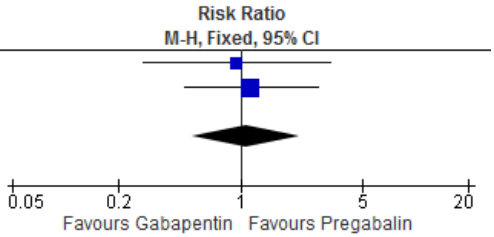


Figure 232: Urinary Retention

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ozgencil 2011	4	30	5	30	100.0%	0.80 [0.24, 2.69]
Total (95% CI)		**30**		**30**	**100.0%**	**0.80 [0.24, 2.69]**
Total events	4		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

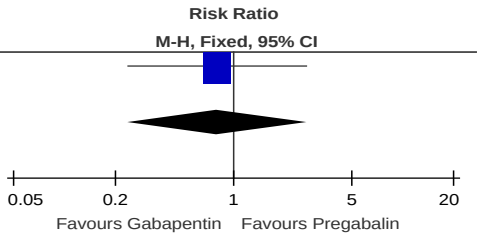


Figure 233: Headache

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ozgencil 2011	5	30	2	30	100.0%	2.50 [0.53, 11.89]
Total (95% CI)		**30**		**30**	**100.0%**	**2.50 [0.53, 11.89]**
Total events	5		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)

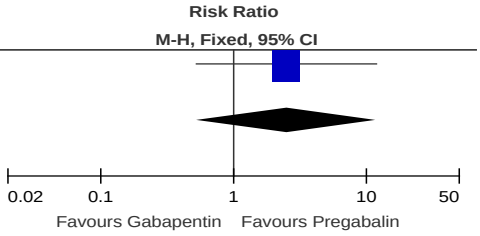


Figure 234: Pruritus

Study or Subgroup	Gabapentin Events	Gabapentin Total	Pregabalin Events	Pregabalin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ozgencil 2011	5	30	4	30	100.0%	1.25 [0.37, 4.21]
Total (95% CI)		**30**		**30**	**100.0%**	**1.25 [0.37, 4.21]**
Total events	5		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

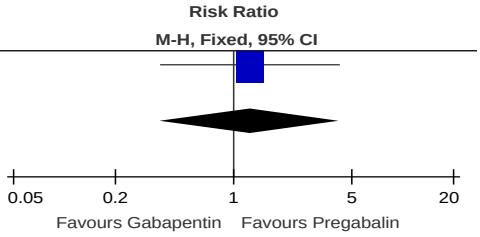
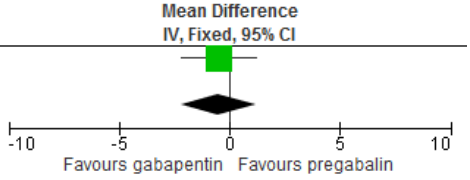


Figure 235: Length of stay

Study or Subgroup	Gabapentin Mean	Gabapentin SD	Gabapentin Total	Pregabalin Mean	Pregabalin SD	Pregabalin Total	Weight	Mean Difference IV, Fixed, 95% CI
Hanoura 2018	6.8	1.9	19	7.3	3.2	18	100.0%	-0.50 [-2.21, 1.21]
Total (95% CI)			**19**			**18**	**100.0%**	**-0.50 [-2.21, 1.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)



D.4 Gabapentin vs Opioid for managing acute post-operative pain

Figure 236: Pain score ≤ 6 hours

Study or Subgroup	Gabapentin Mean	SD	Total	Tramadol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pandey 2004	2.65	3	153	2.97	2.35	153	100.0%	-0.32 [-0.92, 0.28]
Total (95% CI)			**153**			**153**	**100.0%**	**-0.32 [-0.92, 0.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)

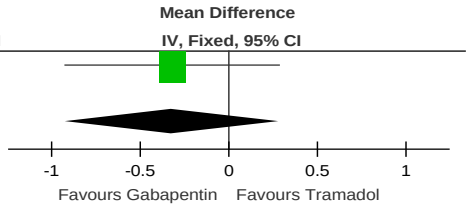


Figure 237: Pain score >6 - 24 hours

Study or Subgroup	Gabapentin Mean	SD	Total	Tramadol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pandey 2004	0.65	3	153	0.87	0.61	153	100.0%	-0.22 [-0.71, 0.27]
Total (95% CI)			**153**			**153**	**100.0%**	**-0.22 [-0.71, 0.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

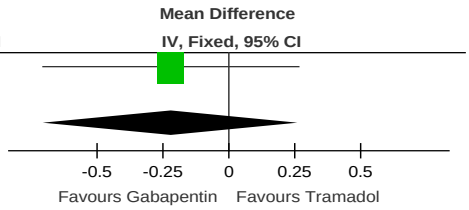


Figure 238: Dose of Opioid consumed >6 - 24 hours

Study or Subgroup	Gabapentin Mean	SD	Total	Tramadol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pandey 2004	221.16	52.39	153	269.6	44.17	153	100.0%	-48.44 [-59.30, -37.58]
Total (95% CI)			**153**			**153**	**100.0%**	**-48.44 [-59.30, -37.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.74 (P < 0.00001)

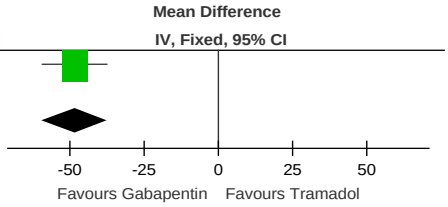


Figure 239: Sedation

Study or Subgroup	Gabapentin Events	Total	Tramadol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pandey 2004	52	153	44	153	100.0%	1.18 [0.85, 1.65]
Total (95% CI)		**153**		**153**	**100.0%**	**1.18 [0.85, 1.65]**
Total events	52		44			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

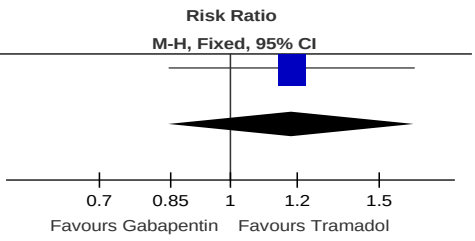
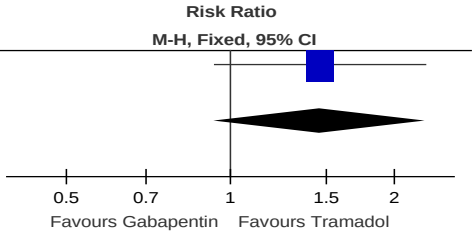


Figure 240: Nausea & Vomiting

Study or Subgroup	Gabapentin Events	Total	Tramadol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pandey 2004	38	153	26	153	100.0%	1.46 [0.94, 2.28]
Total (95% CI)		**153**		**153**	**100.0%**	**1.46 [0.94, 2.28]**
Total events	38		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.10)



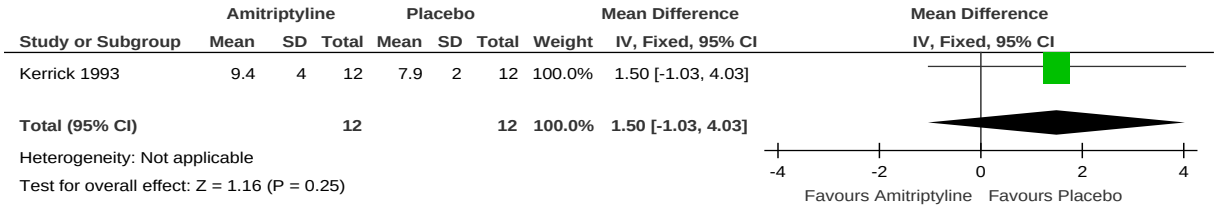
1

Figure 241: Respiratory Depression

2 # D.5 Amitriptyline vs Placebo for managing acute post-operative
3 pain

4

Figure 242: Length of hospital stay



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6

Appendix E: GRADE tables

Table 39: Clinical evidence profile: Gabapentin vs Placebo for managing acute post-operative pain

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute		
Pain score ≤6 hours (follow-up 6 hours; range of scores: 0-10; Better indicated by lower values)												
23	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	serious[2]	none	1000	706	-	MD 1.46 lower (1.91 to 1.01 lower)	⊕OOO VERY LOW	CRITICAL
Pain score 24 hours (follow-up 24 hours; range of scores: 0-10; Better indicated by lower values)												
21	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision[2]	none	929	650	-	MD 0.87 lower (1.29 to 0.46 lower)	⊕⊕OO LOW	CRITICAL
Dose of opioid consumed ≤6h (follow-up 6 hours; Better indicated by lower values)												
9	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	288	272	-	SMD 0.77 lower (1.12 to 0.42 lower)	⊕⊕OO LOW	CRITICAL
Dose of opioid consumed 24h (follow-up 24 hours; Better indicated by lower values)												
30	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision[2]	none	1360	1079	-	SMD 1.80 lower (2.2 to 1.4 lower)	⊕⊕OO LOW	CRITICAL

Respiratory Depression											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/140 (5%)	3.3%	RR 1.06 (0.21 to 5.27)	2 more per 1000 (from 26 fewer to 141 more)	⊕⊕OO LOW	CRITICAL
Nausea ≤6 hours (follow-up 6 hours)											
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	35/91 (38.5%)	40%	RR 1.1 (0.78 to 1.56)	40 more per 1000 (from 88 fewer to 224 more)	⊕⊕OO LOW	CRITICAL
Nausea 24 hours (follow-up 24 hours)											
20	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	143/865 (16.5%)	25%	RR 0.77 (0.63 to 0.95)	58 fewer per 1000 (from 13 fewer to 93 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Vomiting ≤6 hours (follow-up 6 hours)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	23/60 (38.3%)	40%	RR 0.97 (0.67 to 1.4)	12 fewer per 1000 (from 132 fewer to 160 more)	⊕⊕OO LOW	CRITICAL
Vomiting 24 hours (follow-up 24 hours)											
21	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	117/932 (12.6%)	16.7%	RR 0.66 (0.51 to 0.83)	57 fewer per 1000 (from 28 fewer to 82 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Nausea & Vomiting ≤ 6 hours (follow-up 6 hours)											
2	randomised	no serious	serious[1]	no serious	no serious	none	6/92	22.8%	RR 0.32 (0.13	155 fewer per 1000 (from 55 fewer to 198	⊕⊕⊕O	CRITICAL

	trials	risk of bias		indirectness	imprecision		(6.5%)		to 0.76)	fewer)	MODERATE	
Nausea & Vomiting (follow-up . Postoperatively)												
7	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	109/381 (28.6%)	46.7%	RR 0.67 (0.42 to 1.07)	154 fewer per 1000 (from 271 fewer to 33 more)	⊕⊕OO LOW	CRITICAL
Dizziness ≤6 hours (follow-up 6 hours)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	39/183 (21.3%)	23.5%	RR 1.04 (0.69 to 1.56)	9 more per 1000 (from 73 fewer to 132 more)	⊕⊕OO LOW	CRITICAL
Dizziness 24 hours (follow-up 24 hours)												
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	80/652 (12.3%)	7.4%	RR 1.29 (0.95 to 1.77)	21 more per 1000 (from 4 fewer to 57 more)	⊕⊕⊕O MODERATE	CRITICAL
Somnolance ≤ 6 hours (follow-up 6 hours)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20/31 (64.5%)	64.7%	RR 1 (0.7 to 1.43)	0 fewer per 1000 (from 194 fewer to 278 more)	⊕⊕OO LOW	CRITICAL
Somnolance 24 hours (follow-up 24 hours)												
12	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	64/599 (10.7%)	4%	RR 1.72 (0.93 to 3.18)	29 more per 1000 (from 3 fewer to 87 more)	⊕⊕⊕O MODERATE	CRITICAL
Sedation ≤6 hours (follow-up 6 hours)												

2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/92 (12%)	8.7%	RR 1.48 (0.6 to 3.63)	42 more per 1000 (from 35 fewer to 229 more)	⊕⊕OO LOW	CRITICAL
Sedation (follow-up . Postoperatively)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	55/212 (25.9%)	13.3%	RR 1.16 (0.92 to 1.47)	21 more per 1000 (from 11 fewer to 63 more)	⊕⊕⊕O MODERATE	CRITICAL
Urinary Retention (follow-up . Postoperatively)												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	13/219 (5.9%)	2.8%	RR 0.78 (0.42 to 1.47)	6 fewer per 1000 (from 16 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
Dry Mouth (follow-up . Postoperatively)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	37/66 (56.1%)	50%	Peto OR 7.39 (0.15 to 372.38)	381 more per 1000 (from 370 fewer to 497 more)	⊕⊕OO LOW	CRITICAL
Pruritus (follow-up . Postoperatively)												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35/425 (8.2%)	8%	Peto OR 0.62 (0.35 to 1.09)	29 fewer per 1000 (from 50 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
Headache ≤ 6 hours (follow-up 6 hours)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/61 (13.1%)	14.8%	RR 0.91 (0.34 to 2.45)	13 fewer per 1000 (from 98 fewer to 215 more)	⊕⊕OO LOW	CRITICAL

Headache (follow-up . Postoperatively)											
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/286 (3.5%)	7%	Peto OR 0.67 (0.29 to 1.56)	22 fewer per 1000 (from 49 fewer to 35 more)	⊕⊕OO LOW	CRITICAL
Light headed (follow-up . Postoperatively)											
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	46/215 (21.4%)	10%	RR 1.04 (0.77 to 1.39)	4 more per 1000 (from 23 fewer to 39 more)	⊕⊕OO LOW	CRITICAL
Length of stay (Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	19	19	-	MD 0.80 lower (2.32 lower to 0.72 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 40: Clinical evidence profile: Pregabalin vs Placebo for managing acute post-operative pain

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pregabalin**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Pain score ≤6 hours (follow-up 6 Hours; range of scores: 0-10; Better indicated by lower values)												
6	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	serious[2]	none	259	176	-	MD 0.89 lower (1.55 to 0.24 lower)	⊕OOO VERY LOW	CRITICAL

Pain score 24 hours (follow-up 24 hours; range of scores: 0-10; Better indicated by lower values)												
6	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	259	176	-	MD 0.18 lower (0.61 lower to 0.25 higher)	⊕⊕OO LOW	CRITICAL
Dose of opioid consumed ≤6h (follow-up 6 hours; Better indicated by lower values)												
7	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	317	203	-	SMD 0.91 lower (1.75 to 0.07 lower)	⊕⊕OO LOW	CRITICAL
Dose of opioid consumed 24h (follow-up 24 hours; Better indicated by lower values)												
7	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision[2]	none	224	195	-	SMD 1.47 lower (2.26 to 0.69 lower)	⊕⊕OO LOW	CRITICAL
Nausea ≤ 6 hours												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/30 (23.3%)	23.3%	RR 1 (0.4 to 2.5)	0 fewer per 1000 (from 140 fewer to 350 more)	⊕⊕OO LOW	CRITICAL
Nausea 24 hours (follow-up 24 hours)												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	36/226 (15.9%)	20%	RR 0.62 (0.43 to 0.88)	76 fewer per 1000 (from 24 fewer to 114 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Vomiting 24 hours (follow-up 24 hours)												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	38/226 (16.8%)	8.3%	RR 0.52 (0.34 to 0.78)	40 fewer per 1000 (from 18 fewer to 55 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Nausea & Vomiting (follow-up . Postoperatively)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	21/87 (24.1%)	31.7%	RR 1 (0.63 to 1.6)	0 fewer per 1000 (from 117 fewer to 190 more)	⊕⊕OO LOW	CRITICAL
Sedation ≤ 6 hours (follow-up 6 hours)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/30 (3.3%)	0%	Peto Odds 7.39 (0.15 to 372.38)	Not estimable	⊕⊕OO LOW	CRITICAL
Sedation 24 hours (follow-up 24 hours)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/52 (5.8%)	4.2%	Peto Odds 1.71 (0.27 to 10.74)	30 more per 1000 (from 31 fewer to 409 more)	⊕⊕OO LOW	CRITICAL
Ramsay Sedation Score ≤ 6 hours (follow-up 6 hours; range of scores: 0-6; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	120	60	-	MD 0.32 higher (0.1 to 0.54 higher)	⊕⊕⊕O MODERATE	CRITICAL
Ramsay Sedation Score 24hours (follow-up 24 hours; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	60	30	-	MD 0.07 higher (0.08 lower to 0.22 higher)	⊕⊕⊕O MODERATE	CRITICAL
Dizziness ≤ 6 hours (follow-up 6 hours)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	19/111 (17.1%)	5.2%	RR 3 (0.8 to 11.2)	104 more per 1000 (from 10 fewer to 530 more)	⊕⊕⊕O MODERATE	CRITICAL

Dizziness 24 hours (follow-up 24 hours)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	28/160 (17.5%)	15.4%	RR 1.15 (0.66 to 2)	23 more per 1000 (from 52 fewer to 154 more)	⊕⊕OO LOW	CRITICAL
Pruritus (follow-up . Postoperatively)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	13/162 (8%)	15%	RR 0.51 (0.26 to 1.04)	74 fewer per 1000 (from 111 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Urinary Retention (follow-up . Postoperatively)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/82 (6.1%)	12.1%	RR 0.82 (0.31 to 2.2)	22 fewer per 1000 (from 83 fewer to 145 more)	⊕⊕OO LOW	CRITICAL
Respiratory Depression (follow-up . Postoperatively)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/49 (6.1%)	0%	RR 4.32 (0.5 to 37.31)	-	⊕⊕OO LOW	CRITICAL
Headache ≤ 6 hours (follow-up 6 hours)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/30 (16.7%)	13.3%	RR 1.25 (0.37 to 4.21)	33 more per 1000 (from 84 fewer to 427 more)	⊕⊕OO LOW	CRITICAL
Headache 24 hours (follow-up 24 hours)												
3	randomised	no serious	no serious	no serious	very serious[2]	none	13/79	13.3%	RR 1.14 (0.56 to	19 more per 1000 (from 59 fewer to 176	⊕⊕OO	CRITICAL

	trials	risk of bias	inconsistency	indirectness			(16.5%)		2.32)	more)	LOW	
Somnolence (follow-up . Postoperatively)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/78 (5.1%)	3.3%	RR 2.0 (0.48 to 8.35)	33 more per 1000 (from 17 fewer to 243 more)	⊕⊕OO LOW	CRITICAL
Length of stay (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	18	19	-	MD 0.30 lower (2.24 lower to 1.64 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 41: Clinical evidence profile: Gabapentin vs Pregabalin for managing acute post-operative pain

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gabapentin**	**Pregabalin**	**Relative (95% CI)**	**Absolute**		
Pain score ≤6 hours (follow-up 6 hours; range of scores: 0-10; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	serious[2]	none	79	78	-	MD 0.47 lower (1.55 lower to 0.62 higher)	⊕OOO VERY LOW	CRITICAL
Pain score 24 hours (follow-up 24 hours; range of scores: 0-10; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	88	90	-	MD 0.05 higher (0.09 lower to 0.18 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Dose of Opioid <6 hours (Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	36	-	MD 2.80 lower (3.99 to 1.61 lower)	⊕⊕⊕O MODERATE	CRITICAL
Dose of opioid consumed 24h (follow-up 24 hours; Better indicated by lower values)												
7	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	very serious[2]	none	186	186	-	SMD 0.59 higher (1.08 lower to 2.25 higher)	⊕OOO VERY LOW	CRITICAL
Sedation (follow-up . Postoepratively)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	21/85 (24.7%)	20%	RR 0.95 (0.58 to 1.56)	10 fewer per 1000 (from 84 fewer to 112 more)	⊕⊕OO LOW	CRITICAL
Respiratory Depression (follow-up . Postoperatively)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/30 (6.7%)	10%	RR 0.67 (0.12 to 3.71)	33 fewer per 1000 (from 88 fewer to 271 more)	⊕⊕OO LOW	CRITICAL
Nausea (follow-up . Postoperatively)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	26/140 (18.6%)	13.3%	RR 1.03 (0.63 to 1.68)	4 more per 1000 (from 49 fewer to 90 more)	⊕⊕OO LOW	CRITICAL
Vomiting (follow-up . Postoperatively)												
5	randomised	no serious	no serious	no serious	very serious[2]	none	27/140	10%	RR 1.22 (0.76 to	22 more per 1000 (from 24 fewer to 95	⊕⊕OO	CRITICAL

	trials	risk of bias	inconsistency	indirectness			(19.3%)		1.95)	more)	LOW	
Nausea & Vomiting (follow-up . Postoperatively)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/30 (16.7%)	13.3%	RR 1.25 (0.37 to 4.21)	33 more per 1000 (from 84 fewer to 427 more)	⊕⊕OO LOW	CRITICAL
Dizziness (follow-up . Postoperatively)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	18/74 (24.3%)	21.3%	RR 1.19 (0.65 to 2.16)	40 more per 1000 (from 75 fewer to 247 more)	⊕⊕OO LOW	CRITICAL
Somnolance (follow-up . Postoperatively)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/49 (24.5%)	23.3%	RR 1.07 (0.52 to 2.19)	16 more per 1000 (from 112 fewer to 277 more)	⊕⊕OO LOW	CRITICAL
Urine Retention (follow-up . Postoperatively)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/30 (13.3%)	16.7%	RR 0.8 (0.24 to 2.69)	33 fewer per 1000 (from 127 fewer to 282 more)	⊕⊕OO LOW	CRITICAL
Headache (follow-up . Postoperatively)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/30 (16.7%)	6.7%	RR 2.5 (0.53 to 11.89)	101 more per 1000 (from 31 fewer to 730 more)	⊕⊕OO LOW	CRITICAL
Pruritus (follow-up . Postoperatively)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/30 (16.7%)	13.3%	RR 1.25 (0.37 to 4.21)	33 more per 1000 (from 84 fewer to 427 more)	⊕⊕OO LOW	CRITICAL
Length of stay (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	19	18	-	MD 0.50 lower (2.21 lower to 1.21 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 42: Clinical evidence profile: Gabapentin vs Opioid for managing acute post-operative pain

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gabapentin**	**Opioid**	**Relative (95% CI)**	**Absolute**		
Pain score ≤6 hours (follow-up 6 hours; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	153	153	-	MD 0.32 lower (0.92 lower to 0.28 higher)	⊕⊕OO LOW	CRITICAL
Pain score 24 hours (follow-up 24 hours; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	153	153	-	MD 0.22 lower (0.71 lower to 0.27 higher)	⊕⊕OO LOW	CRITICAL
Dose of opioid consumed 24h (follow-up 24 hours; Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	153	153	-	MD 48.44 lower (59.3 to 37.58 lower)	⊕⊕⊕O MODERATE	CRITICAL
Sedation (follow-up . Postoperatively)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	52/153 (34%)	28.8%	RR 1.18 (0.85 to 1.65)	52 more per 1000 (from 43 fewer to 187 more)	⊕⊕OO LOW	CRITICAL
Nausea & Vomiting (follow-up . Postoperatively)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	38/153 (24.8%)	17%	RR 1.46 (0.94 to 2.28)	78 more per 1000 (from 10 fewer to 218 more)	⊕⊕OO LOW	CRITICAL
Respiratory Depression (follow-up . Postoperatively)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/153 (0%)	3.9%	RR 0.08 (0 to 1.35)	36 fewer per 1000 (from 39 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 43: Clinical evidence profile: Amitriptyline vs Placebo for managing acute post-operative pain

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amitriptyline**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Length of hospital stay (follow-up, Postoperatively; Better indicated by lower values)												
1	randomised	no serious risk	no serious	no serious	very	none	12	12	-	MD 1.5 higher (1.03 lower	⊕⊕OO	IMPORTANT

	trials	of bias	inconsistency	indirectness	serious[1]					to 4.03 higher)	LOW	

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix F:Health economic evidence tables

None.

Appendix G: Excluded studies

G.1 Excluded clinical studies

Table 44: Studies excluded from the clinical review

Study	Exclusion reason
Abasivash 2010[1]	Not available
Abbasabadi 2015[2]	Not available
Ahn 2016[17]	Incorrect Intervention
Alayed 2014[26]	Systematic Review – references cross checked
Amr 2010[38]	Incorrect Intervention
Aydogan 2014[59]	Not in English
Bang 2010[72]	Incorrect Intervention
Bartholdy 2006[79]	Incorrect Intervention
Bashir 2011[82]	Not available
Bekawi 2014[93]	Incorrect Intervention
Bharti 2013[103]	Incorrect Intervention
Bhatia 2016[104]	Incorrect Intervention
Bornemann-Cimenti 2012[119]	No relevant outcomes
Boscariol 2007[121]	No relevant outcomes
Brackel 2014[126]	Citation only
Burke 2010[134]	Incorrect Intervention
Butt 2009[136]	Not available
Cabrera Schulmeyer 2010[137]	Incorrect Intervention
Chang 2009[156]	Incorrect Intervention
Chaparro 2012[158]	Incorrect Intervention
Cheng 2009[167]	Not available
Choi 2013[179]	Incorrect Intervention
Chotton 2015[181]	Incorrect Intervention
Clarke 2009[189]	Incorrect study design
Clarke 2010[187]	No relevant outcomes
Clendenen 2010[191]	Incorrect Intervention
Dauri 2009[221]	Systematic Review – references cross checked
Debaecker 2014[227]	Not available
Demirhan 2014[230]	Incorrect Intervention
Demirhan 2013[231]	Incorrect Intervention
Deniz 2012[234]	Incorrect intervention
Dhasmana 2009[240]	Incorrect Intervention
Doleman 2015[247]	Systematic Review – references cross checked
Dolgun 2014[248]	Incorrect study design – cohort study
Dong 2016[249]	Systematic Review – references cross checked
Eipe 2015[264]	Systematic Review – references cross checked
El Sayed El-Gohary 2014[266]	Not available
Engelman 2011[275]	Systematic Review – references cross checked

Study	Exclusion reason
Ercan 2014[276]	Not available
Eskandar 2013[279]	Incorrect Intervention
Fabritius 2017[286]	Systematic Review – references cross checked
Fabritius 2016[285]	Systematic Review – references cross checked
Fatthallah 2012[291]	Not available
Freedman 2008[306]	No relevant outcomes
Frouzanfard 2013[309]	Incorrect Intervention
Ghai 2011[326]	Incorrect Intervention
Ghoneim 2013[330]	Incorrect Intervention
Gilron 2005[333]	Incorrect Intervention
Gilron 2007[332]	Incorrect study design
Gonano 2011[336]	Incorrect Intervention
Grover 2009[350]	No relevant outcomes
Gurunathan 2016[363]	Incorrect Intervention
Hah 2018[368]	Incorrect Intervention
Hamilton 2016[373]	Systematic Review – references cross checked
Han 2017[374]	Systematic Review – references cross checked
Han 2016[375]	Systematic Review – references cross checked
Hegarty 2011[390]	Incorrect Intervention
Ho 2006[399]	Systematic Review – references cross checked
Ho 2008[400]	Incorrect Intervention
Hu 2018[411]	Network Meta Analysis – references cross checked
Huot 2008[417]	Incorrect intervention
Hurley 2006[418]	Systematic Review – references cross checked
Hwang 2016[424]	Systematic Review – references cross checked
Jain 2012[436]	Incorrect Intervention
Jeon 2009[448]	Incorrect Intervention
Jiang 2018[454]	Systematic Review – references cross checked
Jiang 2017[452]	Systematic Review – references cross checked
Jiang 2017[453]	Systematic Review – references cross checked
Joshi 2013[466]	Incorrect Intervention
Karbic 2014[490]	Incorrect intervention
Kim 2011[519]	Incorrect Intervention
Kim 2008[515]	Not available
Kim 2004[526]	Not available
Kim 2014[520]	Incorrect Intervention
Kim 2010[527]	Incorrect Intervention
Kim 2011[528]	Incorrect Intervention
Kinney 2012[529]	Incorrect Intervention
Kjaer Petersen 2018[531]	Incorrect Intervention
Kochhar 2017[538]	Incorrect Intervention
Kochhar 2017[537]	Incorrect Intervention
Kohli 2011[540]	Incorrect Intervention
Konstantatos 2016[543]	Incorrect Intervention
Koşucu 2014[550]	Incorrect Intervention

Study	Exclusion reason
Koyuncu 2013[553]	Not in English
Kuhnle 2011[557]	Incorrect Intervention
Kumar 2013[559]	Incorrect Intervention
Kumari 2009[560]	Incorrect Intervention
Lam 2015[568]	Systematic Review – references cross checked
Lee 2013[585]	Incorrect Intervention
Lee 2013[589]	Incorrect Intervention
Leung 2017[600]	Incorrect Intervention
Leung 2006[601]	Duplicate study
Li 2018[607]	Incorrect Intervention
Li 2017[610]	Systematic Review – references cross checked
Li 2017[609]	Systematic Review – references cross checked
Lichtinger 2011[613]	Incorrect Intervention
Liu 2017[621]	Systematic Review – references cross checked
Lunn 2015[642]	Incorrect Intervention
Luo 2009[643]	Not available
Macheridou 2012[648]	Citation only
Macheridou 2011[649]	Citation only
Mahoori 2014[655]	Incorrect Intervention
Maleh 2013[657]	Not in English
Maleh 2013[657]	Not in English
Mansor 2015[663]	Incorrect Intervention
Mao 2016[666]	Systematic Review – references cross checked
Mardani-Kivi 2013[671]	Duplicate study
Martinez 2014[675]	Incorrect Intervention
Mathiesen 2007[679]	Systematic Review – references cross checked
Mathiesen 2008[678]	Incorrect Intervention
McQuay 2008[696]	Systematic Review – references cross checked
Menda 2010[701]	Incorrect Intervention
Menigaux 2005[704]	Incorrect Intervention
Meurant 2006[716]	Citation only
Mikkelsen 2006[720]	Incorrect Intervention
Mishriky 2015[725]	Systematic Review – references cross checked
Moghimi 2018[735]	Incorrect Intervention
Mohsin 2019[739]	Incorrect intervention
Monks 2015[743]	Incorrect Intervention
Montazeri 2007[745]	Duplicate study
Myhre 2017[781]	Incorrect Intervention
Najafi Anaraki 2014[783]	Incorrect Intervention
Nakhli 2018[784]	Incorrect Intervention
Nantha-Aree 2011[787]	Conference abstract
NCT 2015[861]	Citation only
NCT 2009[821]	Citation only
NCT 2005[790]	Citation only
NCT 2016[871]	Citation only

Study	Exclusion reason
NCT 2009[822]	Citation only
NCT 2010[832]	Citation only
NCT 2013[848]	Citation only
NCT 2009[823]	Citation only
NCT 2014[855]	Citation only
NCT 2017[888]	Citation only
NCT 2010[833]	Citation only
NCT 2007[798]	Citation only
NCT 2008[810]	Citation only
NCT 2008[811]	Citation only
NCT 2007[799]	Citation only
NCT 2009[824]	Citation only
NCT 2009[825]	Citation only
NCT 2011[840]	Citation only
NCT 2013[850]	Citation only
NCT 2016[877]	Citation only
NCT 2007[800]	Citation only
NCT 2010[835]	Citation only
NCT 2015[866]	Citation only
NCT 2009[828]	Citation only
NCT 2008[813]	Citation only
NCT 2016[880]	Citation only
NCT 2012[846]	Citation only
NCT 2008[814]	Citation only
NCT 2008[815]	Citation only
NCT 2011[841]	Citation only
NCT 2008[816]	Citation only
NCT 2008[817]	Citation only
NCT 2008[818]	Citation only
NCT 2014[858]	Citation only
NCT 2008[819]	Citation only
NCT 2007[801]	Citation only
NCT 2010[837]	Citation only
NCT 2007[802]	Citation only
NCT 2016[883]	Citation only
NCT 2009[829]	Citation only
NCT 2007[803]	Citation only
NCT 2009[830]	Citation only
NCT 2007[804]	Citation only
Nimmaanrat 2012[924]	Incorrect Intervention
Olmedo-Gaya 2016[938]	Incorrect Intervention
Omar 2009[942]	Incorrect Intervention
Omran 2005[943]	Not available
Paech 2007[957]	Incorrect Intervention
Pandey 2004[964]	Duplicate study

Study	Exclusion reason
Park 2016[976]	Systematic Review – references cross checked
Park 2015[979]	Incorrect Intervention
Parveen 2016[987]	Incorrect Intervention
Peng 2007[994]	Systematic Review – references cross checked
Peng 2010[993]	Incorrect Intervention
Pesonen 2011[998]	Incorrect Intervention
Pourfakhr 2019[1013]	Incorrect intervention
Poylin 2014[1015]	No relevant outcomes
Qadeer 2017[1021]	Incorrect Intervention
Radwan 2010[1028]	Incorrect Intervention
Rafiq 2014[1030]	Incorrect Intervention
Rai 2017[1032]	Systematic Review – references cross checked
Ram 2015[1033]	Incorrect Intervention
Rapchuk 2010[1035]	Incorrect Intervention
Rascon-Martinez 2018[1036]	Not in English
Rascón-Martínez 2018[1037]	Not in English
Reyes-Perez 2017[1055]	Not in English
Rezaeian 2017[1057]	Incorrect Intervention
Rimaz 2014[1062]	Incorrect Intervention
Rorarius 2004[1067]	Incorrect Intervention
Saeed 2013[1086]	Incorrect Intervention
Sagit 2013[1090]	Incorrect Intervention
Sagit 2013[1090]	Incorrect Intervention
Sanders 2016[1098]	Systematic Review – references cross checked
Sanders 2017[1097]	Incorrect population – patients under 18 included
Sarakatsianou 2013[1102]	No relevant outcomes
Sava 2009[1107]	Not available
Secrist 2016[1119]	Systematic Review – references cross checked
Sekhavat 2009[1121]	Incorrect Intervention
Sen 2009[1123]	Citation only
Sidiropoulou 2016[1143]	Incorrect Intervention
Solak 2007[1177]	Incorrect Intervention
Spence 2011[1184]	Incorrect Intervention
Steagall 2018[1192]	Incorrect study design – animal study
Steinberg 2017[1195]	Systematic Review – references cross checked
Sun 2016[1214]	Systematic Review – references cross checked
Takmaz 2007[1231]	Not available
Tayyem 2017[1248]	Systematic Review – references cross checked
Tiippana 2007[1257]	Systematic Review – references cross checked
Titsworth 2016[1259]	Incorrect study design – before and after
Tiwari 2014[1260]	No relevant outcomes
Tsaousi 2017[1267]	Systematic Review – references cross checked
Turan 2006[1277]	Incorrect Intervention
Ture 2009[1278]	Neurosurgical procedure (protocol exclusion)
Ucak 2011[1283]	Incorrect Intervention

Study	Exclusion reason
Van Elstraete 2008[1304]	Incorrect study design – time trial
Van Haagen 2018[1305]	Incorrect study design – time trial
Wang 2017[1330]	Systematic Review – references cross checked
Wang 2010[1328]	Incorrect Intervention
Warrender 2017[1337]	Systematic Review – references cross checked
Xiude 2010[1373]	Not available
Xudong 2008[1374]	Not in English
Xuliang 2009[1376]	Not available
YaDeau 2015[1379]	Incorrect Intervention
YaDeau 2015[1378]	Incorrect Intervention
Yadeau 2012[1380]	Incorrect Intervention
Yao 2015[1392]	Systematic Review – references cross checked
Yeganeh Mogadam 2012[1399]	Incorrect population (protocol exclusion)
Yoshimura 2015[1407]	Incorrect Intervention
Yu 2013[1415]	Systematic Review – references cross checked
Zakkar 2013[1422]	Systematic Review – references cross checked
Zhai 2016[1431]	Systematic Review – references cross checked
Zhang 2011[1433]	Systematic Review – references cross checked
Zhang 2014[1434]	Incorrect study design – statistical study
Zhang 2016[1432]	Systematic Review – references cross checked
Zhang 2015[1435]	Incorrect study design – statistical study
Zhou 2013[1440]	Not available

G.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 45: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Costs of paracetamol are demonstrated in Table 46.

Table 46: UK costs of paracetamol

Drug	Formulation	Dose	Daily cost	Source of dosage
Paracetamol				
Paracetamol	500mg tablets	4g	£0.04	GC member
Paracetamol	1g/100ml solution for infusion vial	4g	£1.79	GC member
Paracetamol	1g/100ml solution for infusion vial	2g	£0.89	GC member

Source: Electronic market information tool (eMIT), Accessed September 2019[199]

The costs of different types of opioids are demonstrated in Table 46.

Table 47: UK costs of opioids

Drug	Formulation	Daily dose	Daily cost	Source of dosage
Oral administration – modified release				
Morphine	10mg tablets	10mg BD	£0.17[a]	GC Member
Average cost			**£0.17**	
Oral administration – immediate release				
Codeine	30mg tablets	30mg to 60mg QDS	£0.05[b]	GC Member
Hydromorphone	1.3mg capsules	1.3mg QDS	£0.63[a]	GC Member
Morphine	10mg tablets	10mg (every 4 hours)	£0.54[b]	BNF
Morphine sulphate	10mg/5ml oral solution	10mg to 20mg QDS	£0.21[a]	GC Member
Oxycodone	5mg tablets	5mg TDS	£0.06[b]	GC Member
Tramadol	50mg tablets	50mg to 100mg QDS	£0.02[b]	GC Member
Average cost			**£0.24**	
Intravenous administration				
Fentanyl	100micorgrams/2ml solution for injection ampoules	250micrograms	£0.54[b]	GC Member
Morphine	10mg/1ml solution for injection ampoules	120mg	£2.84[b]	GC Member
Average cost			**£1.69**	
Patient controlled analgesia				
Morphine	50mg/50ml solution for infusion vials	180mg	£10.12[b]	GC member
Fentanyl	100micrograms/2ml solution for injection ampoules	1.5mg	£2.69[a]	GC member

Drug	Formulation	Daily dose	Daily cost	Source of dosage
Oxycodone	20mg/2ml solution for injection ampoules	180mg	£9.48[a]	GC member
Average cost			**£7.43**	
Spinal epidural (single shot)				
Diamorphine	10mg powder for solution for injection ampoules	10mg	£2.86[b]	GC member
Fentanyl	100micrograms/2ml solution for injection ampoules	50 micrograms	£0.09[b]	GC member
Average cost			**£1.48**	
Continuous epidural				
Bupivicaine with fentanyl	1mg/ml and 2micrograms/ml 250ml infusion bags	250ml bupivacaine 0.1% with fentanyl 2 micrograms/ml	£17.00[a]	GC member
Average cost			**£17.00**	

Sources:
(a) British National Formulary, Accessed September 2019[457]
(b) Electronic market information tool (eMIT), Accessed September 2019[199]
Abbreviations: BD = twice daily; QDS = 4 times daily

The costs of different types of non-steroidal anti-inflammatories and COX-2 inhibitors are demonstrated in Table 48.

Table 48: UK costs of NSAIDs and COX-2 inhibitors

Drug	*Formulation*	Daily dose	Daily cost	Source of dosage
Non-steroidal anti-inflammatory drugs				
Diclofenac	50mg tablet	150mg	£0.11[(a)]	GC member
	75mg/3ml solution for injection	150mg	£1.49[(a)]	BNF
Ibuprofen	200mg tablet	1200mg	£0.04[(a)]	GC member
Ketorolac	30mg/1ml solution for injection	10mg to 30mg	£0.43[(a)]	GC member
Naproxen	500mg tablet	1000mg	£0.05[(a)]	GC member
COX-2 inhibitors				
Celecoxib	100mg tablet	200mg	£0.04[(a)]	GC member
Parecoxib	40mg powder for injection	80mg	£11.34[(b)]	BNF

Sources:
(c) Electronic market information tool (eMIT), Accessed September 2019[199]
(d) British National Formulary, Accessed September 2019[457]

The costs of ketamine are demonstrated in Table 49.

Table 49: UK costs of ketamine

Drug	Formulation	Daily dose	Daily cost	Source of dosage
Ketamine				
Ketamine	500mg/10ml solution for injection vials	500mg	**£2.83**	GC Member

Source: Electronic market information tool (eMIT), Accessed September 2019[199]

The costs of neuropathic nerve stabilisers are demonstrated in Table 50.

Table 50: UK costs of neuropathic nerve stabilisers

Drug	Formulation	Daily dose	Daily cost	Source of dosage
Neuropathic nerve stabilisers				
Amitriptylin	10 mg tablet	10mg	£0.03[(a)]	GC Member
Gabapentin	300 mg tablet	900mg	£0.05[(a)]	GC Member
Nortriptylline	25 mg tablet	50mg	£0.17[(b)]	GC Member
Pregabalin	50mg tablet	150mg	£0.12[(b)]	GC Member
Average cost			**£0.09**	

Sources:
(a) Electronic market information tool (eMIT), Accessed September 2019[199]
(b) British National Formulary, Accessed September 2019[457]

Some forms of administration result in additional costs associated with disposables. Table 51 shows the disposable costs associated with these different forms of administration.

Table 51: UK costs of disposables

Equipment	Cost per person	Source
Intravenous administration		
1 x Cannula (Venflon)	£0.86	NHS Supply Chain[916]
2 x 10ml syringe	£0.45	
1 x syringe bung	£0.51	
1 x Cliniwipe Disinfectant Wipe	£0.02	
1 x IV dressing	£0.90	
1 x drawing up needle	£0.45	
1 x Sodium chloride 0.9%	£0.04	Electronic market information tool (eMIT)[199]
Total cost	**£3.23**	
Patient-controlled analgesia		
1 x PCA administration set	£11.62[a]	NHS Supply Chain[916]
1 x fluid administration set	£0.04	
1 x Cannula (Venflon)	£0.86	
1 x 50ml syringe	£0.89	
1 x 10ml syringe	£0.22	
1 x Sodium chloride 0.9%	£0.04	Electronic market information tool (eMIT)[199]

Equipment	Cost per person	Source
Total cost	**£13.67**	
Continuous epidural		
1 x epidural administration set	£9.59[(b)]	NHS Supply Chain[916]
1 x transpore surgical tape	£0.81	
1 x Mepore dressing	£0.43	
1 x Gauze	£0.14	
Total cost	**£10.97**	
Spinal epidural (single shot)		
1 x epidural administration set	£9.59[(b)]	NHS Supply Chain[916]
1 x transpore surgical tape	£0.81	
1 x Mepore dressing	£0.43	
1 x Gauze	£0.14	
Total cost	**£10.97**	

(a)Cost is based on the average cost of all administration sets for PCA pumps listed in the NHS Supply Chain catalogue

(b) Cost is based on the average cost of all epidural administration sets listed in the NHS Supply Chain catalogue

The total daily costs associated with each form of administration are demonstrated below.

Table 52: Total daily costs of analgesics

Analgesic	Total daily cost per person[(a)]
Oral paracetamol	£0.04
Intravenous paracetamol	£5.02
Oral NSAIDs	£0.07
Intravenous NSAIDs	£4.19
Oral COX-2 inhibitors	£0.04
Intravenous COX-2 inhibitors	£14.57
Oral opioid	£0.24
Intravenous opioid	£4.92
Patient-controlled analgesia	£21.10
Continuous epidural	£27.97
Spinal epidural	£12.45
Neuropathic nerve stabilisers	£0.09
Intravenous ketamine	£6.06

(a) The total daily cost was obtained using a straight average across the different types of each analgesic

Literature search strategies

This literature search strategy was used for the following review questions:

- **What is the clinical and cost effectiveness of IV paracetamol compared to oral paracetamol given post operatively in managing acute post-operative pain?**
- **What is the clinical and cost effectiveness of adding IV paracetamol to IV opioids given intraoperatively in managing acute post-operative pain?**
- **What is the clinical and cost effectiveness of NSAIDs for managing acute postoperative pain?**
- **What is the clinical and cost effectiveness of IV opioid compared to oral opioid given post operatively in managing acute post-operative pain?**
- **What is the most clinically and cost effective opioid administration strategy?**
- **What is the clinical and cost effectiveness of adding IV ketamine to iv opioids in managing acute post-operative pain?**
- **What is the clinical and cost effectiveness of neuropathic nerve stabilisers in managing acute post-operative pain?**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2018.[788]

For more detailed information, please see the Methodology Review.]

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 53: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 30 May 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 30 May 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	postoperative care/ or exp Postoperative Period/ or exp perioperative nursing/
2.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine or pain)).ti,ab.
3.	((care* or caring or treat* or nurs* or recover* or monitor* or pain) adj3 after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
4.	Pain, Postoperative/
5.	Intraoperative Care/ or exp Intraoperative Period/
6.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
7.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 during adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
11.	9 not 10
12.	letter/
13.	editorial/
14.	news/
15.	exp historical article/
16.	Anecdotes as Topic/
17.	comment/
18.	case report/
19.	(letter or comment*).ti.
20.	or/12-19
21.	randomized controlled trial/ or random*.ti,ab.
22.	20 not 21
23.	animals/ not humans/
24.	exp Animals, Laboratory/
25.	exp Animal Experimentation/
26.	exp Models, Animal/
27.	exp Rodentia/
28.	(rat or rats or mouse or mice).ti.
29.	or/22-28
30.	11 not 29
31.	Acetaminophen/
32.	(acetaminophen or paracetamol).ti,ab.
33.	analgesics, opioid/
34.	(Opioid* or Opiate*).ti,ab.
35.	(morphine or morphia or msir).ti,ab.
36.	exp morphinans/
37.	(opium or omnopon or pantopon or papaveretum).ti,ab.
38.	(dihydromorphinone or hydromorph*).ti,ab.
39.	(oxycodone or dihydrohydroxycodeinone or dihydrone or oxycone or oxycontin).ti,ab.
40.	(Dihydrocodeine or dihydcdn).ti,ab.
41.	(Diamorphine or acetomorphine or diacetylmorphine or heroin).ti,ab.

42.	(Codeine or ardinex or galcodine or isocodeine or methyl morphine).ti,ab.
43.	(Pethidine or isonipecain or isonipecaine hydrochloride or meperidine).ti,ab.
44.	Meperidine/
45.	(Fentanyl or fentanil or fentyl or phentanyl).ti,ab.
46.	Fentanyl/
47.	Dextromoramide.ti,ab.
48.	Dextromoramide/
49.	(Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).ti,ab.
50.	Pirinitramide/
51.	(Dextropropoxyphene or levopropoxyphene or propoxyphene or proxyphen).ti,ab.
52.	Dextropropoxyphene/
53.	exp Methadone/
54.	(methadone or amidone).ti,ab.
55.	Pentazocine.ti,ab.
56.	Phenazocine.ti,ab.
57.	Oripavine.ti,ab.
58.	Buprenorphine.ti,ab.
59.	Butorphanol/
60.	Butorphanol.ti,ab.
61.	(tilid* or valoron).ti,ab.
62.	Tramadol/
63.	Tilidine/
64.	(Tramadol or tramal*).ti,ab.
65.	Dezocine.ti,ab.
66.	meptazinol/
67.	Meptazinol.ti,ab.
68.	(Tapentadol or cg5503).ti,ab.
69.	(Remifentanil or 'gi 87084b' or remifentanyl).ti,ab.
70.	(alfentanil or alfentanyl).ti,ab.
71.	(gabapentin* or pregabalin*).ti,ab.
72.	Alfentanil/
73.	Pregabalin/
74.	(neuropathic adj3 analges*).ti,ab.
75.	(nortriptyline or amitriptyline).ti,ab.
76.	Amitriptyline/
77.	Nortriptyline/
78.	Ketamine/
79.	(ketamine or keta).ti,ab.
80.	exp anti-inflammatory agents, non-steroidal/
81.	(nsaid* or ((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory))).ti,ab.
82.	(cox adj2 inhibitor*).ti,ab.
83.	coxibs.ti,ab.
84.	((cyclooxygenase or cyclo oxygenase) adj2 inhibitor*).ti,ab.
85.	exp Prostaglandin-Endoperoxide Synthases/

86.	(prostaglandin* adj2 (synthase* or synthesis or cyclooxygenase or cyclo oxygenase)).ti,ab.
87.	(ibuprofen or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or dichlofenal or aceclofenac or indometacin or indomethacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or etodolac or rofecoxib).ti,ab.
88.	or/31-87
89.	30 and 88
90.	randomized controlled trial.pt.
91.	controlled clinical trial.pt.
92.	randomi#ed.ab.
93.	placebo.ab.
94.	randomly.ab.
95.	clinical trials as topic.sh.
96.	trial.ti.
97.	or/90-96
98.	Meta-Analysis/
99.	Meta-Analysis as Topic/
100.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
101.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
102.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
103.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
104.	(search* adj4 literature).ab.
105.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
106.	cochrane.jw.
107.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
108.	or/98-107
109.	89 and (97 or 108)

1 **Embase (Ovid) search terms**

1.	*postoperative care/ or *postoperative period/ or *perioperative nursing/ or *surgical patient/
2.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine or pain)).ti,ab.
3.	((care* or caring or treat* or nurs* or recover* or monitor* or pain) adj3 after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
4.	*Postoperative Pain/
5.	*peroperative care/ or *intraoperative period/ or *surgical patient/
6.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
7.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 during adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)

11.	9 not 10
12.	letter.pt. or letter/
13.	note.pt.
14.	editorial.pt.
15.	case report/ or case study/
16.	(letter or comment*).ti.
17.	or/12-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animal/ not human/
21.	nonhuman/
22.	exp Animal Experiment/
23.	exp Experimental Animal/
24.	animal model/
25.	exp Rodent/
26.	(rat or rats or mouse or mice).ti.
27.	or/19-26
28.	11 not 27
29.	*paracetamol/
30.	(acetaminophen or paracetamol).ti,ab.
31.	*opiate/
32.	(Opioid* or Opiate*).ti,ab.
33.	(morphine or morphia or msir).ti,ab.
34.	exp *morphinan derivative/
35.	(opium or omnopon or pantopon or papaveretum).ti,ab.
36.	(dihydromorphinone or hydromorph*).ti,ab.
37.	(oxycodone or dihydrohydroxycodeinone or dihydrone or oxycone or oxycontin).ti,ab.
38.	exp *morphine derivative/
39.	(Dihydrocodeine or dihydcdn).ti,ab.
40.	(Diamorphine or acetomorphine or diacetylmorphine or heroin).ti,ab.
41.	(Codeine or ardinex or galcodine or isocodeine or methyl morphine).ti,ab.
42.	(Pethidine or isonipecain or isonipecaine hydrochloride or meperidine).ti,ab.
43.	*pethidine/
44.	(Fentanyl or fentanil or fentyl or phentanyl).ti,ab.
45.	*fentanyl/
46.	Dextromoramide.ti,ab.
47.	*dextromoramide/
48.	(Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).ti,ab.
49.	*piritramide/
50.	(Dextropropoxyphene or levopropoxyphene or propoxyphene or proxyphen).ti,ab.
51.	(methadone or amidone).ti,ab.
52.	*methadone/
53.	Pentazocine.ti,ab.
54.	*pentazocine/
55.	Phenazocine.ti,ab.

56.	*Phenazocine/
57.	Oripavine.ti,ab.
58.	Buprenorphine.ti,ab.
59.	Butorphanol.ti,ab.
60.	(tilid* or valoron).ti,ab.
61.	*tilidine/
62.	(Tramadol or tramal*).ti,ab.
63.	*tramadol/
64.	Dezocine.ti,ab.
65.	*dezocine/
66.	Meptazinol.ti,ab.
67.	*meptazinol/
68.	(Tapentadol or cg5503).ti,ab.
69.	*tapentadol/
70.	(Remifentanil or 'gi 87084b' or remifentanyl).ti,ab.
71.	*remifentanil/
72.	(alfentanil or alfentanyl).ti,ab.
73.	alfentanil/
74.	(gabapentin* or pregabalin*).ti,ab.
75.	*pregabalin/
76.	(neuropathic adj3 analges*).ti,ab.
77.	(nortriptyline or amitriptyline).ti,ab.
78.	*amitriptyline/
79.	*nortriptyline/
80.	(ketamine or keta).ti,ab.
81.	ketamine/
82.	*ketamine/
83.	exp *narcotic analgesic agent/
84.	*nonsteroid antiinflammatory agent/ or aceclofenac/ or acemetacin/ or alclofenac/ or celecoxib/ or dexibuprofen/ or dexketoprofen/ or diclofenac/ or etodolac/ or etoricoxib/ or fenoprofen/ or flurbiprofen/ or ibuprofen/ or indometacin/ or ketoprofen/ or ketorolac/ or mefenamic acid/ or meloxicam/ or nabumetone/ or naproxen/ or phenylbutazone/ or piroxicam/ or rofecoxib/ or sulindac/ or tenoxicam/ or tiaprofenic acid/ or tolfenamic acid/
85.	(nsaid* or ((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory))).ti,ab.
86.	(cox adj2 inhibitor*).ti,ab.
87.	coxibs.ti,ab.
88.	((cyclooxygenase or cyclo oxygenase) adj2 inhibitor*).ti,ab.
89.	(prostaglandin* adj2 (synthase* or synthesis or cyclooxygenase or cyclo oxygenase)).ti,ab.
90.	*prostaglandin synthase/
91.	(ibuprofen or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or dichlofenal or aceclofenac or indometacin or indomethacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or etodolac or rofecoxib).ti,ab.
92.	or/29-91

93.	random*.ti,ab.
94.	factorial*.ti,ab.
95.	(crossover* or cross over*).ti,ab.
96.	((doubl* or singl*) adj blind*).ti,ab.
97.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
98.	crossover procedure/
99.	single blind procedure/
100.	randomized controlled trial/
101.	double blind procedure/
102.	or/93-101
103.	systematic review/
104.	Meta-Analysis/
105.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
106.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
107.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
108.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
109.	(search* adj4 literature).ab.
110.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
111.	cochrane.jw.
112.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
113.	or/103-112
114.	28 and 92
115.	114 and (102 or 113)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Postoperative Care] this term only
#2.	MeSH descriptor: [Postoperative Period] this term only
#3.	MeSH descriptor: [Perioperative Nursing] this term only
#4.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) near/3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine or pain)):ti,ab
#5.	((care* or caring or treat* or nurs* or recover* or monitor* or pain) near/3 after near/3 (surg* or operat* or anaesthes* or anesthes*)):ti,ab
#6.	MeSH descriptor: [Pain, Postoperative] this term only
#7.	MeSH descriptor: [Intraoperative Care] this term only
#8.	MeSH descriptor: [Intraoperative Period] explode all trees
#9.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) near/3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)):ti,ab
#10.	((care* or caring or treat* or nurs* or recover* or monitor*) near/3 (during) near/3 (surg* or operat* or anaesthes* or anesthes*)):ti,ab
#11.	(or #1-#10)
#12.	MeSH descriptor: [Acetaminophen] this term only
#13.	(acetaminophen or paracetamol):ti,ab
#14.	MeSH descriptor: [Analgesics, Opioid] this term only
#15.	(Opioid* or Opiate*):ti,ab

#16.	(morphine or morphia or msir):ti,ab
#17.	MeSH descriptor: [Morphinans] explode all trees
#18.	(opium or omnopon or pantopon or papaveretum):ti,ab
#19.	(dihydromorphinone or hydromorph*):ti,ab
#20.	(oxycodone or dihydrohydroxycodeinone or dihydrone or oxycone or oxycontin):ti,ab
#21.	(Dihydrocodeine or dihydcdn):ti,ab
#22.	(Diamorphine or acetomorphine or diacetylmorphine or heroin):ti,ab
#23.	(Codeine or ardinex or galcodine or isocodeine or methyl morphine):ti,ab
#24.	(Pethidine or isonipecain or isonipecaine hydrochloride or meperidine):ti,ab
#25.	MeSH descriptor: [Meperidine] explode all trees
#26.	(Fentanyl or fentanil or fentyl or phentanyl):ti,ab
#27.	MeSH descriptor: [Fentanyl] this term only
#28.	Dextromoramide:ti,ab
#29.	MeSH descriptor: [Dextromoramide] this term only
#30.	(Piritramide or Dipidolor or dipydolor or Piridolan or Pirium):ti,ab
#31.	MeSH descriptor: [Pirinitramide] this term only
#32.	(Dextropropoxyphene or levopropoxyphene or propoxyphene or proxyphen):ti,ab
#33.	MeSH descriptor: [Dextropropoxyphene] this term only
#34.	(methadone or amidone):ti,ab
#35.	MeSH descriptor: [Methadone] explode all trees
#36.	Pentazocine:ti,ab
#37.	Phenazocine:ti,ab
#38.	Oripavine:ti,ab
#39.	Buprenorphine:ti,ab
#40.	MeSH descriptor: [Butorphanol] this term only
#41.	Butorphanol:ti,ab
#42.	(tilid* or valoron):ti,ab
#43.	MeSH descriptor: [Tilidine] this term only
#44.	(Tramadol or tramal*):ti,ab
#45.	MeSH descriptor: [Tramadol] explode all trees
#46.	Dezocine:ti,ab
#47.	MeSH descriptor: [Meptazinol] this term only
#48.	Meptazinol:ti,ab
#49.	(Tapentadol or cg5503):ti,ab
#50.	(Remifentanil or gi 87084b or remifentanyl):ti,ab
#51.	(alfentanil or alfentanyl):ti,ab
#52.	MeSH descriptor: [Alfentanil] this term only
#53.	(gabapentin* or pregabalin*):ti,ab
#54.	MeSH descriptor: [Pregabalin] this term only
#55.	(neuropathic near/3 analges*):ti,ab
#56.	(nortriptyline or amitriptyline):ti,ab
#57.	MeSH descriptor: [Nortriptyline] this term only
#58.	MeSH descriptor: [Amitriptyline] this term only
#59.	MeSH descriptor: [Ketamine] this term only
#60.	(ketamine or keta):ti,ab

#61.	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#62.	(nsaid* or ((non-steroid* or nonsteroid*) near/1 (antiinflammatory or anti-inflammatory))):ti,ab
#63.	(cox near/2 inhibitor*):ti,ab
#64.	coxibs:ti,ab
#65.	((cyclooxygenase or cyclo oxygenase) near/2 inhibitor*):ti,ab
#66.	MeSH descriptor: [Prostaglandin-Endoperoxide Synthases] explode all trees
#67.	(prostaglandin* near/2 (synthase* or synthesis or cyclooxygenase or cyclo oxygenase)):ti,ab
#68.	(ibuprofen or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or dichlofenal or aceclofenac or indometacin or indomethacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or etodolac or rofecoxib):ti,ab
#69.	(or #12-#68)
#70.	#11 and #69

Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the perioperative care population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

Table 54: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 May 2019	Exclusions Health economics studies
Embase	2014 – 30 May 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 02 May 2019 NHSEED - Inception to 02 May 2019	None

Medline (Ovid) search terms

1.	exp Preoperative Care/ or exp Perioperative Care/ or exp Perioperative Period/ or exp Perioperative Nursing/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
5.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
6.	1 or 2 or 3 or 4 or 5
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.

8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	7 or 8
10.	postoperative care/ or exp Postoperative Period/ or exp Perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp Preoperative Care/ or Preoperative Period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	6 or 9 or 14 or 18
20.	letter/
21.	editorial/
22.	news/
23.	exp historical article/
24.	Anecdotes as Topic/
25.	comment/
26.	case report/
27.	(letter or comment*).ti.
28.	or/20-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animals/ not humans/
32.	exp Animals, Laboratory/
33.	exp Animal Experimentation/
34.	exp Models, Animal/
35.	exp Rodentia/
36.	(rat or rats or mouse or mice).ti.
37.	or/30-36
38.	19 not 37
39.	limit 38 to English language
40.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
41.	39 not 40
42.	economics/
43.	value of life/
44.	exp "costs and cost analysis"/
45.	exp Economics, Hospital/
46.	exp Economics, medical/
47.	Economics, nursing/
48.	economics, pharmaceutical/
49.	exp "Fees and Charges"/
50.	exp budgets/

51.	budget*.ti,ab.
52.	cost*.ti.
53.	(economic* or pharmaco?economic*).ti.
54.	(price* or pricing*).ti,ab.
55.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
56.	(financ* or fee or fees).ti,ab.
57.	(value adj2 (money or monetary)).ti,ab.
58.	or/42-57
59.	41 and 58

1 **Embase (Ovid) search terms**

1.	*preoperative period/ or *intraoperative period/ or *postoperative period/ or *perioperative nursing/ or *surgical patient/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
5.	1 or 2 or 3 or 4
6.	peroperative care/ or exp peroperative care/ or exp perioperative nursing/
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	6 or 7 or 8
10.	postoperative care/ or exp postoperative period/ or perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp preoperative care/ or preoperative period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	5 or 9 or 14 or 18
20.	letter.pt. or letter/
21.	note.pt.
22.	editorial.pt.
23.	case report/ or case study/
24.	(letter or comment*).ti.
25.	or/20-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26

28.	animal/ not human/
29.	nonhuman/
30.	exp Animal Experiment/
31.	exp Experimental Animal/
32.	animal model/
33.	exp Rodent/
34.	(rat or rats or mouse or mice).ti.
35.	or/27-34
36.	19 not 35
37.	limit 36 to English language
38.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
39.	37 not 38
40.	health economics/
41.	exp economic evaluation/
42.	exp health care cost/
43.	exp fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	39 and 53

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Preoperative Care EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Perioperative Care EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Perioperative Period EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Perioperative Nursing EXPLODE ALL TREES
#5.	(((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#6.	(((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#7.	(((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#8.	(((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	(* IN HTA)

#11.	(* IN NHSEED)
#12.	#9 AND #10
#13.	#9 AND #11
#14.	MeSH DESCRIPTOR Intraoperative Care EXPLODE ALL TREES
#15.	#1 OR #2 OR #3 OR #4 OR #14
#16.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*))
#17.	(((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#18.	((postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*))
#19.	((after adj3 (surg* or operat* or anaesthes* or anesthes*)))
#20.	((post adj3 (operat* or anaesthes* or anesthes*)))
#21.	((pre-operat* or preoperat* or pre-surg* or presurg*))
#22.	(((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#23.	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24.	#10 AND #23
#25.	#11 AND #23
#26.	#12 OR #13 OR #24 OR #25

1

References

1. Abasivash R, Heshmati F, Noroozinia H, Poorghasem J, Ghazi SF. The effect of a single dose of gabapentin on the rate of consumption of propofol and remifentanil during total intravenous anesthesia. Scientific Journal of Kurdistan University of Medical Sciences. 2010; 15(3):40-48

2. Abbasabadi FM, Emadi S, Baradari AG, Alipour A, Pashakolai GA, Hashemi SA. Effect of single dose and low dose of pregabalin on postoperative pain of abdominal hysterectomy. International Journal of Review in Life Sciences. 2015; 5:780-784

3. Abd-Elsayed AA, Guirguis M, DeWood MS, Zaky SS. A Double-Blind Randomized Controlled Trial Comparing Epidural Clonidine vs Bupivacaine for Pain Control During and After Lower Abdominal Surgery. Ochsner Journal. 2015; 15(2):133-42

4. Abdel-Ghaffar HS, Kalefa MA, Imbaby AS. Efficacy of ketamine as an adjunct to lidocaine in intravenous regional anesthesia. Regional Anesthesia and Pain Medicine. 2014; 39(5):418-22

5. Abdelmageed W, Abdelrazik S, Nassar A, Abdelkawi M. Analgesic effects of gabapentine in tonsillectomy. The Egyptian Journal of Hospital Medicine. 2010; 38(1):51-58

6. Abdolahi M, Soltani HA, Montazeri K, Soleymani B. Preemptive low-dose of ketamine does not effective on anesthetic consumption, perioperative analgesic requirement and postoperative pain, nausea and vomiting in painful ophthalmic surgery. Journal of Research in Medical Sciences. 2013; 18(7):583-7

7. Abrishamkar S, Eshraghi N, Feizi A, Talakoub R, Rafiei A, Rahmani P. Analgesic effects of ketamine infusion on postoperative pain after fusion and instrumentation of the lumbar spine: a prospective randomized clinical trial. Medicinski Arhiv. 2012; 66(2):107-10

8. Abuzaid H, Prys-Roberts C, Wilkins DG, Terry DM. The influence of diamorphine on spinal anaesthesia induced with isobaric 0.5% bupivacaine. Anaesthesia. 1993; 48(6):492-5

9. Aceto P, Clemente A, Sicilia F, De Cosmo G. Comparison between intravenous patient-controlled analgesia and epidural analgesia in patients undergoing lower abdominal surgery. Acta Medica Romana. 2002; 40(1):3-11

10. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesthesia and Analgesia. 2005; 100(2):475-80

11. Adriaenssens G, Vermeyen KM, Hoffmann VL, Mertens E, Adriaensen HF. Postoperative analgesia with i.v. patient-controlled morphine: effect of adding ketamine. British Journal of Anaesthesia. 1999; 83(3):393-6

12. Aftab S, Rashdi S. Comparison of intravenous ketorolac with diclofenac for postoperative analgesia. Journal of Surgery Pakistan. 2008; 13(2):62-66

13. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. British Journal of Anaesthesia. 2008; 101(5):700-4

14. Agarwal A, Sinha PK, Pandey CM, Gaur A, Pandey CK, Kaushik S. Effect of a subanesthetic dose of intravenous ketamine and/or local anesthetic infiltration on

hemodynamic responses to skull-pin placement: a prospective, placebo-controlled, randomized, double-blind study. Journal of Neurosurgical Anesthesiology. 2001; 13(3):189-94

15. Aguilar JL, Montes A, Samper D, Roca G, Preciado MJ. Comparison between fentanyl and a fentanyl-bupivacaine combination using epidural PCA for postoperative analgesia after thoracotomy. Revista Española de Anestesióloga y Reanimación. 1994; 41(3):165-167

16. Ahlstrom U, Bakshi R, Nilsson P, Wahlander L. The analgesic efficacy of diclofenac dispersible and ibuprofen in postoperative pain after dental extraction. European Journal of Clinical Pharmacology. 1993; 44(6):587-8

17. Ahn S, Byun SH, Park K, Ha JL, Kwon B, Kim JC. Analgesic efficacy of preemptive pregabalin administration in arthroscopic shoulder surgery: a randomized controlled trial. Canadian Journal of Anaesthesia. 2016; 63(3):283-9

18. Aida S, Yamakura T, Baba H, Taga K, Fukuda S, Shimoji K. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: a randomized double-blind study. Anesthesiology. 2000; 92(6):1624-30

19. Ajori L, Nazari L, Mazloomfard MM, Amiri Z. Effects of gabapentin on postoperative pain, nausea and vomiting after abdominal hysterectomy: a double blind randomized clinical trial. Archives of Gynecology and Obstetrics. 2012; 285(3):677-82

20. Akhavanakbari G, Mohamadian A, Entezariasl M. Evaluation the effects of adding ketamine to morphine in intravenous patient-controlled analgesia after orthopedic surgery. Perspectives in Clinical Research. 2014; 5(2):85-7

21. Akinbade AO, Ndukwe KC, Owotade FJ. Comparative analgesic effects of ibuprofen, celecoxib and tramadol after third molar surgery: a randomized double blind controlled trial. Journal of Contemporary Dental Practice. 2018; 19(11):1334-1340

22. Al-Mujadi H, AR AR, Katzarov MG, Dehrab NA, Batra YK, Al-Qattan AR. Preemptive gabapentin reduces postoperative pain and opioid demand following thyroid surgery. Canadian Journal of Anaesthesia. 2006; 53(3):268-73

23. Al-Sukhun J, Al-Sukhun S, Penttila H, Ashammakhi N, Al-Sukhun R. Preemptive analgesic effect of low doses of celecoxib is superior to low doses of traditional nonsteroidal anti-inflammatory drugs. Journal of Craniofacial Surgery. 2012; 23(2):526-529

24. Al-Sukhun J, Penttila H. The cyclooxygenase-2 inhibitor celecoxib and alveolar osteitis. Journal of the Irish Dental Association. 2011; 57(1):50-53

25. Alanoglu Z, Ates Y, Orbey BC, Turkcapar AG. Preoperative use of selective COX-II inhibitors for pain management in laparoscopic nissen fundoplication. Surgical Endoscopy. 2005; 19(9):1182-7

26. Alayed N, Alghanaim N, Tan X, Tulandi T. Preemptive use of gabapentin in abdominal hysterectomy: a systematic review and meta-analysis. Obstetrics and Gynecology. 2014; 123(6):1221-9

27. Albert JM, Talbott TM. Patient-controlled analgesia vs. conventional intramuscular analgesia following colon surgery. Diseases of the Colon and Rectum. 1988; 31(2):83-6

28. Albuquerque AFM, Fonteles CSR, do Val DR, Chaves HV, Bezerra MM, Pereira KMA et al. Effect of pre-emptive analgesia on clinical parameters and tissue levels of TNF-alpha and IL-1beta in third molar surgery: a triple-blind, randomized, placebo-

controlled study. International Journal of Oral and Maxillofacial Surgery. 2017; 46(12):1615-1625

29. Alexander JI, Kong KL, Black AMS. Epidural and intravenous infusions of diamorphine. European Journal of Anaesthesiology. 1990; 7(4):309-315

30. Ali M, Khan FA. Comparison of analgesic effect of tramadol alone and a combination of tramadol and paracetamol in day-care laparoscopic surgery. European Journal of Anaesthesiology. 2009; 26(6):475-9

31. Ali S, Zarin M, Jan Z, Maroof A. Effect of bupivacaine on postoperative pain after laparoscopic cholecystectomy. Journal of College of Physicians and Surgeons Pakistan. 2018; 28(9):663-666

32. Alimian M, Imani F, Hassani V, Rahimzadeh P, Sharifian M, Safari S. Effects of single-dose pregabalin on postoperative pain in dacryocystorhinostomy surgery. Anesthesiology & Pain Medicine. 2012; 2(2):72-6

33. Alimian M, Pournajafian A, Kholdebarin A, Ghodraty M, Rokhtabnak F, Yazdkhasti P. Analgesic effects of paracetamol and morphine after elective laparotomy surgeries. Anesthesiology & Pain Medicine. 2014; 4(2):e12912

34. Allaire PH, Messick JM, Jr., Oesterling JE, Byer DE, Myers RP, Lieber MM et al. A prospective randomized comparison of epidural infusion of fentanyl and intravenous administration of morphine by patient-controlled analgesia after radical retropubic prostatectomy. Mayo Clinic Proceedings. 1992; 67(11):1031-41

35. Alon E, Jaquenod M, Schaeppi B. Post-operative epidural versus intravenous patient-controlled analgesia. Minerva Anestesiologica. 2003; 69(5):443-6

36. Alonso Chico A, Cruz Pardos P, Alvarez Grau J, Pachoco Jiménez A, Arregui Martínez de Lejarza M, Sánchez García ML et al. Comparison of the hemodynamic response in subarachnoid anesthesia with bupivacaine versus bupivacaine with fentanyl in traumatology surgery in elderly patients. Revista Española de Anestesióloga y Reanimación. 2003; 50(1):17-22

37. Altun D, Cinar O, Ozker E, Turkoz A. The effect of tramadol plus paracetamol on consumption of morphine after coronary artery bypass grafting. Journal of Clinical Anesthesia. 2017; 36:189-193

38. Amr YM, Yousef AA. Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. Clinical Journal of Pain. 2010; 26(5):381-5

39. Amr YM, Yousef AA, Alzeftawy AE, Messbah WI, Saber AM. Effect of preincisional epidural fentanyl and bupivacaine on postthoracotomy pain and pulmonary function. Annals of Thoracic Surgery. 2010; 89(2):381-5

40. Andonov N, Hristova J, Teneva V, Spirovska T, Micevski M. Continuous epidural analgesia with morphine and ketamine for postoperative pain relief. British Journal of Anaesthesia. 1998; 80 (Suppl 1):173

41. Andreoni C, Olweny EO, Portis AJ, Sundaram CP, Monk T, Clayman RV. Effect of single-dose subarachnoid spinal anesthesia on pain and recovery after unilateral percutaneous nephrolithotomy. Journal of Endourology. 2002; 16(10):721-725

42. Api O, Unal O, Ugurel V, Emeksiz MB, Turan C. Analgesic efficacy of intravenous paracetamol for outpatient fractional curettage: a randomised, controlled trial. International Journal of Clinical Practice. 2009; 63(1):105-11

43. Aqil M, Ul-Haq A, Rasheed A, Hussain A, Khan M, Al-Saeed A. Is preemptive analgesic effect of ketamine dose dependent? effect of increasing dose on post septorhinoplasty pain. Pakistan Journal of Medical Sciences. 2011; 27(3):608-612

44. Araimo Morselli FS, Zuccarini F, Caporlingua F, Scarpa I, Imperiale C, Caporlingua A et al. Intrathecal versus intravenous morphine in minimally invasive posterior lumbar fusion: A blinded randomized comparative prospective study. Spine. 2017; 42(5):281-284

45. Argiriadou H, Himmelseher S, Papagiannopoulou P, Georgiou M, Kanakoudis F, Giala M et al. Improvement of pain treatment after major abdominal surgery by intravenous S+-ketamine. Anesthesia and Analgesia. 2004; 98(5):1413-8

46. Argiriadou H, Papagiannopoulou P, Foroulis CN, Anastasiadis K, Thomaidou E, Papakonstantinou C et al. Intraoperative infusion of S(+)-ketamine enhances post-thoracotomy pain control compared with perioperative parecoxib when used in conjunction with thoracic paravertebral ropivacaine infusion. Journal of Cardiothoracic and Vascular Anesthesia. 2011; 25(3):455-61

47. Argoff C, McCarberg B, Gudin J, Nalamachu S, Young C. SoluMatrix diclofenac: sustained opioid-sparing effects in a phase 3 study in patients with postoperative pain. Pain Medicine. 2016; 17(10):1933-1941

48. Arikan M, Aslan B, Arikan O, Horasanli E, But A. Comparison of the effects of magnesium and ketamine on postoperative pain and morphine consumption. A double-blind randomized controlled clinical study. Acta Cirurgica Brasileira. 2016; 31(1):67-73

49. Arnold JD. Ketoprofen, ibuprofen, and placebo in the relief of postoperative pain. Advances in Therapy. 1990; 7(5):264-275

50. Arponrat P, Pongrojpaw D, Tanprasertkul C, Suwannarurk K, Bhamarapravatana K. Postoperative pain relief in major gynaecological surgery by perioperative parecoxib administration: Thammasat University Hospital study. Journal of the Medical Association of Thailand. 2015; 98(7):636-42

51. Asantila R, Eklund P, Rosenberg PH. Continuous epidural infusion of bupivacaine and morphine for postoperative analgesia after hysterectomy. Acta Anaesthesiologica Scandinavica. 1991; 35(6):513-7

52. Assouline B, Tramer MR, Kreienbuhl L, Elia N. Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. Pain. 2016; 157(12):2854-2864

53. Atallah MM, Shorrab AA, Abdel Mageed YM, Demian AD. Low-dose bupivacaine spinal anaesthesia for percutaneous nephrolithotomy: the suitability and impact of adding intrathecal fentanyl. Acta Anaesthesiologica Scandinavica. 2006; 50(7):798-803

54. Atanasova MP. Effect of a single-dose Ketamine administered intraoperatively on the pain and mood in the postoperative period after colorectal surgery. Anaesthesiology and Intensive Care. 2015; 44(1):18-20

55. Atangana R, Ngowe Ngowe M, Binam F, Sosso MA. Morphine versus morphine-ketamine association in the management of post operative pain in thoracic surgery. Acta Anaesthesiologica Belgica. 2007; 58(2):125-7

56. Aubrun F, Gaillat C, Rosenthal D, Dupuis M, Mottet P, Marchetti F et al. Effect of a low-dose ketamine regimen on pain, mood, cognitive function and memory after

major gynaecological surgery: a randomized, double-blind, placebo-controlled trial. European Journal of Anaesthesiology. 2008; 25(2):97-105

57. Aveline C, Gautier JF, Vautier P, Cognet F, Hetet HL, Attali JY et al. Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam. European Journal of Pain. 2009; 13(6):613-9

58. Aveline C, Hetet HL, Vautier P, Gautier JF, Bonnet F. Peroperative ketamine and morphine for postoperative pain control after lumbar disk surgery. European Journal of Pain. 2006; 10(7):653-8

59. Aydogan H, Kucuk A, Yuce HH, Karahan MA, Ciftci H, Gulum M et al. Adding 75 mg pregabalin to analgesic regimen reduces pain scores and opioid consumption in adults following percutaneous nephrolithotomy. Revista Brasileira de Anestesiologia. 2014; 64(5):335-342

60. Aydogan MS, Bicakcioglu M, Sayan H, Durmus M, Yilmaz S. Effects of two different techniques of postoperative analgesia management in liver transplant donors: a prospective, randomized, double-blind study. Transplantation Proceedings. 2015; 47(4):1204-6

61. Ayoglu H, Karadeniz U, Kunduracilar Z, Ayoglu FN, Erdemli O. The analgesic effect of magnesium sulfate and ketamine in patients undergoing laparoscopic cholecystectomy. Pain Clinic. 2005; 17(1):45-53

62. Azad SC, Groh J, Beyer A, Schneck D, Dreher E, Peter K. Continuous epidural analgesia versus patient controlled intravenous analgesia for postthoracotomy pain Acute Pain. 2000; 3(2):14-23

63. Aziz L, Habibur Rahman M, Iqbal KM. A comparative study of tramadol, diclofenac and ketorolac infusion in the management of post-operative pain. Journal of Anaesthesiology Clinical Pharmacology. 2003; 19(2):187-192

64. Badner NH, Bhandari R, Komar WE. Bupivacaine 0.125% improves continuous postoperative epidural fentanyl analgesia after abdominal or thoracic surgery. Canadian Journal of Anaesthesia. 1994; 41(5 Pt 1):387-92

65. Badner NH, Komar WE. Bupivacaine 0.1% does not improve post-operative epidural fentanyl analgesia after abdominal or thoracic surgery. Canadian Journal of Anaesthesia. 1992; 39(4):330-6

66. Badrinath S, Avramov MN, Shadrick M, Witt TR, Ivankovich AD. The use of a ketamine-propofol combination during monitored anesthesia care. Anesthesia and Analgesia. 2000; 90(4):858-62

67. Bainbridge D, Martin JE, Cheng DC. Patient-controlled versus nurse-controlled analgesia after cardiac surgery--a meta-analysis. Canadian Journal of Anaesthesia. 2006; 53(5):492-9

68. Bakshi R, Frenkel G, Dietlein G, Meurer-Witt B, Schneider B, Sinterhauf U. A placebo-controlled comparative evaluation of diclofenac dispersible versus ibuprofen in postoperative pain after third molar surgery. Journal of Clinical Pharmacology. 1994; 34(3):225-30

69. Balaban F, Yagar S, Ozgok A, Koc M, Gullapoglu H. A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. Journal of Clinical Anesthesia. 2012; 24(3):175-178

70. Ballantyne JC, Carr DB, Chalmers TC, Dear KBG, Angelillo IF, Mosteller F. Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. Journal of Clinical Anesthesia. 1993; 5(3):182-193

71. Bameshki A, Peivandi Yazdi A, Sheybani S, Rezaei Boroujerdi H, Taghavi Gilani M. The assessment of addition of either intravenous paracetamol or diclofenac suppositories to patient-controlled morphine analgesia for postgastrectomy pain control. Anesthesiology & Pain Medicine. 2015; 5(5):e29688

72. Bang SR, Yu SK, Kim TH. Can gabapentin help reduce postoperative pain in arthroscopic rotator cuff repair? A prospective, randomized, double-blind study. Arthroscopy. 2010; 26(9 Suppl):S106-11

73. Banning AM, Schmidt JF, Chraemmer-Jorgensen B, Risbo A. Comparison of oral controlled release morphine and epidural morphine in the management of postoperative pain. Anesthesia and Analgesia. 1986; 65(4):385-8

74. Barber FA, Herbert MA. The effectiveness of an anesthetic continuous-infusion device on postoperative pain control. Arthroscopy. 2002; 18(1):76-81

75. Barden J, Edwards JE, McQuay HJ, Moore RA. Single dose oral celecoxib for postoperative pain. Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD004233. DOI: 10.1002/14651858.CD004233.

76. Barnes WH, Pennock MM, Browne GB, Taylor W, Sackett D, Weir R et al. The effect of routine vs. p.r.n. post-operative analgesia on pulmonary complications: a multicenter trial. Canadian Journal of Nursing Research. 1991; 23(4):7-22

77. Barratt SM, Smith RC, Kee AJ, Mather LE, Cousins MJ. Multimodal analgesia and intravenous nutrition preserves total body protein following major upper gastrointestinal surgery. Regional Anesthesia and Pain Medicine. 2002; 27(1):15-22

78. Barreveld AM, Correll DJ, Liu X, Max B, McGowan JA, Shovel L et al. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. Pain Medicine. 2013; 14(6):925-34

79. Bartholdy J, Hilsted KL, Hjortsoe NC, Engbaek J, Dahl JB. Effect of gabapentin on morphine demand and pain after laparoscopic sterilization using Filshie clips. A double blind randomized clinical trial. BMC Anesthesiology. 2006; 6 12

80. Barton SF, Langeland FF, Snabes MC, LeComte D, Kuss ME, Dhadda SS et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. Anesthesiology. 2002; 97(2):306-14

81. Barzoi G, Carluccio S, Bianchi B, Vassia S, Colucci G, Mangiante GL. Morphine plus bupivacaine vs. morphine peridural analgesia in abdominal surgery: the effects on postoperative course in major hepatobiliary surgery. HPB Surgery. 2000; 11(6):393-9

82. Bashir F, Mohd K, Qazi S. A randomized double blind placebo controlled study of prophylactic gabapentin for prevention of postoperative pain and morphine consumption in patients undergoing mastectomy. The Internet Journal of Anesthesiology. 2011; 30(1)

83. Batra YK, Mahajan R, Bangalia SK, Nagi ON, Dhillon MS. Bupivacaine/ketamine is superior to intra-articular ketamine analgesia following arthroscopic knee surgery. Canadian Journal of Anaesthesia. 2005; 52(8):832-6

84. Baubillier E, Leppert C, Delaunay L, Bonnet F. Patient-controlled analgesia: effect of adding continuous infusion of morphine. Annales Françaises d'Anesthésie et de Réanimation. 1992; 11(5):479-483

85. Bauchat JR, Higgins N, Wojciechowski KG, McCarthy RJ, Toledo P, Wong CA. Low-dose ketamine with multimodal postcesarean delivery analgesia: a randomized controlled trial. International Journal of Obstetric Anesthesia. 2011; 20(1):3-9

86. Bauduin H, Famaey JP. Comparison of the analgesic effects of beta-cyclodextrin-piroxicam, sodium naproxen, and potassium diclofenac utilizing the dental pain model. Journal of Pharmaceutical Care in Pain and Symptom Control. 1995; 3(2):19-29

87. Baxter AD, Laganiere S, Samson B, Stewart J, Hull K, Goernert L. A comparison of lumbar epidural and intravenous fentanyl infusions for post-thoracotomy analgesia. Canadian Journal of Anaesthesia. 1994; 41(3):184-91

88. Beaudoin FL, Lin C, Guan W, Merchant RC. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: results of a randomized, double-blind, clinical trial. Academic Emergency Medicine. 2014; 21(11):1193-202

89. Bedder MD, Soifer BE, Mulhall JJ. A comparison of patient-controlled analgesia and bolus PRN intravenous morphine in the intensive care environment. Clinical Journal of Pain. 1991; 7(3):205-8

90. Behdad S, Ayatollahi V, Bafghi AT, Tezerjani MD, Abrishamkar M. Effect of gabapentin on postoperative pain and operation complications: a randomized placebo controlled trial. West Indian Medical Journal. 2012; 61(2):128-33

91. Behdad S, Hajiesmaeili MR, Abbasi HR, Ayatollahi V, Khadiv Z, Sedaghat A. Analgesic effects of intravenous ketamine during spinal anesthesia in pregnant women undergone caesarean section; a randomized clinical trial. Anesthesiology & Pain Medicine. 2013; 3(2):230-3

92. Beilin B, Rusabrov Y, Shapira Y, Roytblat L, Greemberg L, Yardeni IZ et al. Low-dose ketamine affects immune responses in humans during the early postoperative period. British Journal of Anaesthesia. 2007; 99(4):522-7

93. Bekawi MS, El Wakeel LM, Al Taher WM, Mageed WM. Clinical study evaluating pregabalin efficacy and tolerability for pain management in patients undergoing laparoscopic cholecystectomy. Clinical Journal of Pain. 2014; 30(11):944-52

94. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiologica Scandinavica. 2005; 49(10):1405-28

95. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane database of systematic reviews (online) 2006, Issue 1. Art. No.: CD004603. DOI: 10.1002/14651858.CD004603.pub2.

96. Bell S, Rennie T, Marwick C, Davey P. Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function. Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD011274. DOI: 10.1002/14651858.CD011274.pub2.

97. Bennett M, Bonanno L, Kuhn W. Effectiveness of ketamine as an adjuvant to opioid-based therapy in decreasing pain associated with opioid tolerance in adults undergoing orthopedic surgery: a systematic review protocol. JBI Database Of Systematic Reviews And Implementation Reports. 2016; 14(10):22-28

98. Benzon HT, Wong HY, Belavic AM, Jr., Goodman I, Mitchell D, Lefheit T et al. A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. Anesthesia and Analgesia. 1993; 76(2):316-22

99. Bernard JM, Bourreli B, Pinaud M. Effects of systemic morphine and epidural bupivacaine on postoperative oxygen consumption during rewarming. Journal of Clinical Anesthesia. 1988; 1(2):81-86

100. Bernard JM, Hommeril JL, Legendre MP, Passuti N, Pinaud M. Spinal or systemic analgesia after extensive spinal surgery: comparison between intrathecal morphine and intravenous fentanyl plus clonidine. Journal of Clinical Anesthesia. 1993; 5(3):231-236

101. Bertini L, Mancini S, Di Benedetto P, Ciaschi A, Martini O, Nava S et al. Postoperative analgesia by combined continuous infusion and patient-controlled epidural analgesia (PCEA) following hip replacement: ropivacaine versus bupivacaine. Acta Anaesthesiologica Scandinavica. 2001; 45(6):782-5

102. Bertini L, Tagariello V, Molino FM, Posteraro CM, Mancini S, Rossignoli L. Patient-controlled postoperative analgesia in orthopedic surgery: epidural PCA versus intravenous PCA. Minerva Anestesiologica. 1995; 61(7-8):319-328

103. Bharti N, Bala I, Narayan V, Singh G. Effect of gabapentin pretreatment on propofol consumption, hemodynamic variables, and postoperative pain relief in breast cancer surgery. Acta Anaesthesiologica Taiwanica. 2013; 51(1):10-3

104. Bhatia U, Panchal M, Gupta N. To evaluate the role of Gabapentin as preemptive analgesic in patients undergoing total abdominal hysterectomy in spinal anesthesia. European Journal of General Medicine. 2016; 13(4):97-100

105. Bhattacharya A, Gurnani A, Sharma PK, Sethi AK. Subcutaneous infusion of ketamine and morphine for relief of postoperative pain: a double-blind comparative study. Annals of the Academy of Medicine, Singapore. 1994; 23(4):456-9

106. Bialka S, Copik M, Daszkiewicz A, Rivas E, Ruetzler K, Szarpak L et al. Comparison of different methods of postoperative analgesia after thoracotomy-a randomized controlled trial. Journal of Thoracic Disease. 2018; 10(8):4874-4882

107. Bikhazi GB, Snabes MC, Bajwa ZH, Davis DJ, LeComte D, Traylor L et al. A clinical trial demonstrates the analgesic activity of intravenous parecoxib sodium compared with ketorolac or morphine after gynecologic surgery with laparotomy. American Journal of Obstetrics and Gynecology. 2004; 191(4):1183-91

108. Bilgen S, Koner O, Ture H, Menda F, Ficicioglu C, Aykac B. Effect of three different doses of ketamine prior to general anaesthesia on postoperative pain following Caesarean delivery: a prospective randomized study. Minerva Anestesiologica. 2012; 78(4):442-9

109. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Jr., Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003; 290(18):2455-63

110. Blumenthal S, Borgeat A, Nadig M, Min K. Postoperative analgesia after anterior correction of thoracic scoliosis: a prospective randomized study comparing continuous double epidural catheter technique with intravenous morphine. Spine. 2006; 31(15):1646-51

111. Blumenthal S, Min K, Nadig M, Borgeat A. Double epidural catheter with ropivacaine versus intravenous morphine: a comparison for postoperative analgesia after scoliosis correction surgery. Anesthesiology. 2005; 102(1):175-80

112. Boezaart AP, Eksteen JA, Spuy GV, Rossouw P, Knipe M. Intrathecal morphine. Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. Spine. 1999; 24(11):1131-7

113. Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for cesarean section. BMC Anesthesiology. 2005; 5:5

114. Bois S, Couture P, Boudreault D, Lacombe P, Fugere F, Girard D et al. Epidural analgesia and intravenous patient-controlled analgesia result in similar rates of postoperative myocardial ischemia after aortic surgery. Anesthesia and Analgesia. 1997; 85(6):1233-9

115. Boldt J, Thaler E, Lehmann A, Papsdorf M, Isgro F. Pain management in cardiac surgery patients: comparison between standard therapy and patient-controlled analgesia regimen. Journal of Cardiothoracic and Vascular Anesthesia. 1998; 12(6):654-8

116. Bollish SJ, Collins CL, Kirking DM, Bartlett RH. Efficacy of patient-controlled versus conventional analgesia for postoperative pain. Clinical Pharmacy. 1985; 4(1):48-52

117. Bonnal A, Dehon A, Nagot N, Macioce V, Nogue E, Morau E. Patient-controlled oral analgesia versus nurse-controlled parenteral analgesia after caesarean section: a randomised controlled trial. Anaesthesia. 2016; 71(5):535-43

118. Boonriong T, Tangtrakulwanich B, Glabglay P, Nimmaanrat S. Comparing etoricoxib and celecoxib for preemptive analgesia for acute postoperative pain in patients undergoing arthroscopic anterior cruciate ligament reconstruction: a randomized controlled trial. BMC Musculoskeletal Disorders. 2010; 11:246

119. Bornemann-Cimenti H, Lederer AJ, Wejbora M, Michaeli K, Kern-Pirsch C, Archan S et al. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. British Journal of Anaesthesia. 2012; 108(5):845-9

120. Borner M, Bürkle H, Trojan S, Horoshun G, Riewendt HD, Wappler F. Intra-articular ketamine after arthroscopic knee surgery. Optimisation of postoperative analgesia. Der Anaesthesist. 2007; 56(11):1120-1127

121. Boscariol R, Gilron I, Orr E. Chronobiological characteristics of postoperative pain: diurnal variation of both static and dynamic pain and effects of analgesic therapy. Canadian Journal of Anaesthesia. 2007; 54(9):696-704

122. Bouchard F, Drolet P. Thoracic versus lumbar administration of fentanyl using patient-controlled epidural after thoracotomy. Regional Anesthesia. 1995; 20(5):385-8

123. Bourke M, Hayes A, Doyle M, McCarroll M. A comparison of regularly administered sustained release oral morphine with intramuscular morphine for control of postoperative pain. Anesthesia and Analgesia. 2000; 90(2):427-30

124. Bowdle TA, Ready LB, Kharasch ED, Nichols WW, Cox K. Transition to post-operative epidural or patient-controlled intravenous analgesia following total intravenous anaesthesia with remifentanil and propofol for abdominal surgery. European Journal of Anaesthesiology. 1997; 14(4):374-9

125. Boylan JF, Katz J, Kavanagh BP, Klinck JR, Cheng DC, DeMajo WC et al. Epidural bupivacaine-morphine analgesia versus patient-controlled analgesia following abdominal aortic surgery: analgesic, respiratory, and myocardial effects. Anesthesiology. 1998; 89(3):585-93

126. Brackel AML, Marting LN, Timmerman L. Comparison of local infiltration analgesia with epidural analgesia after total knee arthroplasty: a randomized clinical trial (NCT01489631). Dutch Society of Anesthesiology. 2014;

127. Braga Ade F, Braga FS, Hirata ES, Pereira RI, Frias JA, Antunes IF. Association of lipophilic opioids and hyperbaric bupivacaine in spinal anesthesia for elective cesarean section. Randomized controlled study. Acta Cirurgica Brasileira. 2014; 29(11):752-8

128. Bredtmann RD, Kniesel B, Herden HN, Teichmann W. The effect of continuous thoracic peridural anesthesia on the pulmonary function of patients undergoing colon surgery. Results of a randomized study of 116 patients. Regional-Anaesthesie. 1991; 14(1):2-8

129. Briggs GG, Berman ML, Lange S, Riker J, Rettenmaier M, DiSaia P. Morphine: continuous intravenous infusion versus intramuscular injections for postoperative pain relief. Gynecologic Oncology. 1985; 22(3):288-93

130. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA et al. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD012033. DOI: 10.1002/14651858.CD012033.pub4.

131. Bristow A, Orlikowski C. Subcutaneous ketamine analgesia: postoperative analgesia using subcutaneous infusions of ketamine and morphine. Annals of the Royal College of Surgeons of England. 1989; 71(1):64-6

132. Brown CR, Moodie J, Bisley-Phillips E. Bromfenac sodium, naproxen sodium, and ketorolac in moderate to severe postoperative pain. Journal of Pharmaceutical Care in Pain and Symptom Control. 1997; 5(1):21-35

133. Brown JD, Daniels SE, Bandy DP, Ko AT, Gammaitoni A, Mehta A et al. Evaluation of multiday analgesia with etoricoxib in a double-blind, randomized controlled trial using the postoperative third-molar extraction dental pain model. Clinical Journal of Pain. 2013; 29(6):492-8

134. Burke SM, Shorten GD. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. Anesthesia and Analgesia. 2010; 110(4):1180-5

135. Burstal R, Danjoux G, Hayes C, Lantry G. PCA ketamine and morphine after abdominal hysterectomy. Anaesthesia and Intensive Care. 2001; 29(3):246-51

136. Butt A, Mohammad K, Ommid M, Ahmad M, Jehan N, Qazi S. A randomized, double blind placebo controlled study evaluating preventive role of gabapentin for PONV in patients undergoing laparascopic cholecystectomy. Journal of Medical Education & Research. 2009; 11(4):4

137. Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I. Analgesic effects of a single preoperative dose of pregabalin after laparoscopic sleeve gastrectomy. Obesity Surgery. 2010; 20(12):1678-81

138. Cadavid-Puentes A, Bermudez-Guerrero FJ, Giraldo-Salazar O, Munoz-Zapata F, Otalvaro-Henao J, Ruiz-Sierra J et al. Comparison of the effectiveness of fentanyl versus morphine for severe postoperative pain management. A randomized, double blind, clinical trial. Revista Colombiana de Anestesiologia. 2017; 45(2):100-107

139. Cagla Ozbakis Akkurt B, Inanoglu K, Kalaci A, Turhanoglu S, Asfuroglu Z, Tumkaya F. Effects of intravenous small dose ketamine and midazolam on postoperative pain following knee arthroscopy. Pain Practice. 2009; 9(4):289-95

140. Callesen T, Schouenborg L, Nielsen D, Guldager H, Kehlet H. Combined epidural-spinal opioid-free anaesthesia and analgesia for hysterectomy. British Journal of Anaesthesia. 1999; 82(6):881-5

141. Campbell A, McCormick M, McKinlay K, Scott NB. Epidural vs. lumbar plexus infusions following total knee arthroplasty: randomized controlled trial. European Journal of Anaesthesiology. 2008; 25(6):502-7

142. Camu F, Debucquoi F. Comparative profiles of epidural and intravenous continuous infusions of alfentanil in post-operative pain. European Journal of Anaesthesiology. 1991; 8:413-414

143. Canadell-Carafi J, Moreno-Londono A, Fernadez-Fairen M, Vilarrubias-Guillamet JM, Gonzalez-Caudevilla B. Ketorolac 10 mg suppository q.i.d. versus diclofenac 100 mg suppository b.i.d. in post-operative orthopaedic pain. A double-blind comparative analgesic and safety study. Clinical Trials Journal. 1990; 27(6):351-358

144. Canbay O, Celebi N, Uzun S, Sahin A, Celiker V, Aypar U. Topical ketamine and morphine for post-tonsillectomy pain. European Journal of Anaesthesiology. 2008; 25(4):287-292

145. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology. 1999; 91(1):8-15

146. Caranza R, Teyapalan I, Buggy DJ. Central neuraxial opioid analgesia after caesarean section: Comparison of epidural diamorphine and intrathecal morphine. International Journal of Obstetric Anesthesia. 1999; 8(2):90-93

147. Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. Anesthesiology. 2002; 97(3):540-9

148. Carli F, Trudel JL, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomized trial. Diseases of the Colon and Rectum. 2001; 44(8):1083-9

149. Carstensen M, Moller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. British Journal of Anaesthesia. 2010; 104(4):401-6

150. Cassady JF, Jr., Lederhaas G, Cancel DD, Cummings RJ, Loveless EA. A randomized comparison of the effects of continuous thoracic epidural analgesia and intravenous patient-controlled analgesia after posterior spinal fusion in adolescents. Regional Anesthesia and Pain Medicine. 2000; 25(3):246-53

151. Cattabriga I, Pacini D, Lamazza G, Talarico F, Di Bartolomeo R, Grillone G et al. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial. European Journal of Cardio-Thoracic Surgery. 2007; 32(3):527-31

152. Cengiz P, Gokcinar D, Karabeyoglu I, Topcu H, Cicek GS, Gogus N. Intraoperative low-dose ketamine infusion reduces acute postoperative pain following total knee replacement surgery: a prospective, randomized double-blind placebo-controlled trial. Journal of College of Physicians and Surgeons Pakistan. 2014; 24(5):299-303

153. Cha MH, Eom JH, Lee YS, Kim WY, Park YC, Min SH et al. Beneficial effects of adding ketamine to intravenous patient-controlled analgesia with fentanyl after the Nuss procedure in pediatric patients. Yonsei Medical Journal. 2012; 53(2):427-432

154. Chan R. Cochrane review summary: oxycodone or oxycodone plus paracetamol for acute postoperative pain in adults. Journal of Pain Management. 2011; 4(4):439-441

155. Chang AM, Ip WY, Cheung TH. Patient-controlled analgesia versus conventional intramuscular injection: a cost-effectiveness analysis. Journal of Advanced Nursing. 2004; 46(5):531-541

156. Chang SH, Lee HW, Kim HK, Kim SH, Kim DK. An evaluation of perioperative pregabalin for prevention and attenuation of postoperative shoulder pain after laparoscopic cholecystectomy. Anesthesia and Analgesia. 2009; 109(4):1284-6

157. Chang SH, Shin BH, Chae BK, Kong MH, Jo H. Continuous epidural infusion of fentanyl bupivacaine mixtures for analgesia after thoracotomy. Korean Journal of Anesthesiology. 1991; 24(6):1198-1205

158. Chaparro LE, Clarke H, Valdes PA, Mira M, Duque L, Mitsakakis N. Adding pregabalin to a multimodal analgesic regimen does not reduce pain scores following cosmetic surgery: a randomized trial. Journal of Anesthesia. 2012; 26(6):829-35

159. Chapman SJ, Garner JJ, Drake TM, Aldaffaa M, Jayne DG. Systematic review and meta-analysis of nonsteroidal anti-inflammatory drugs to improve GI recovery after colorectal surgery. Diseases of the Colon and Rectum. 2019; 62(2):248-256

160. Charghi R, Backman S, Christou N, Rouah F, Schricker T. Patient controlled iv analgesia is an acceptable pain management strategy in morbidly obese patients undergoing gastric bypass surgery. A restrospective comparison with epidural analgesia. Canadian Journal of Anesthesia. 2003; 50(7):672-678

161. Chauvin M, Hongnat JM, Mourgeon E, Lebrault C, Bellenfant F, Alfonsi P. Equivalence of postoperative analgesia with patient-controlled intravenous or epidural alfentanil. Anesthesia and Analgesia. 1993; 76(6):1251-8

162. Chazan S, Buda I, Nesher N, Paz J, Weinbroum AA. Low-dose ketamine via intravenous patient-controlled analgesia device after various transthoracic procedures improves analgesia and patient and family satisfaction. Pain Management Nursing. 2010; 11(3):169-76

163. Chen JY, Bai L, Yu YF, Zhou SJ. Effects of low dose ketamine during anesthesia on postoperative analgesia. Fudan University Journal of Medical Sciences. 2004; 31(1):81-83

164. Chen LK, Lin PL, Lin CJ, Huang CH, Liu WC, Fan SZ et al. Patient -controlled epidural ropivacaine as a post-cesarean analgesia: a comparison with epidural morphine. Taiwanese Journal of Obstetrics & Gynecology. 2011; 50(4):441-6

165. Chen WK, Ren L, Wei Y, Zhu DX, Miao CH, Xu JM. General anesthesia combined with epidural anesthesia ameliorates the effect of fast-track surgery by mitigating immunosuppression and facilitating intestinal functional recovery in colon cancer patients. International Journal of Colorectal Disease. 2015; 30(4):475-81

166. Cheng PGB, Lim MJ, Onsiong MK, Chiu KYW, Chan MK, Li KWM et al. Celecoxib premedication in post-operative analgesia for laparoscopic cholecystectomy. Acute Pain. 2004; 6(1):23-28

167. Cheng Y, Xiong Y-C. Effect of gabapentin on postoperative pain during anaesthetic period of laparoscopic cholecystectomy. Academic Journal of Second Military Medical University. 2009; 29(8):972-974

168. Cheung CW, Ching Wong SS, Qiu Q, Wang X. Oral oxycodone for acute postoperative pain: A review of clinical trials. Pain Physician. 2017; 20(2S):SE33-SE52

169. Cheung R, Krishnaswami S, Kowalski K. Analgesic efficacy of celecoxib in postoperative oral surgery pain: a single-dose, two-center, randomized, double-blind, active- and placebo-controlled study. Clinical Therapeutics. 2007; 29 (Suppl):2498-510

170. Chi X, Li M, Mei W, Liao M. Comparison of patient-controlled intravenous analgesia with sufentanil versus tramadol in post-cesarean section pain management and lactation after general anesthesia - a prospective, randomized, double-blind, controlled study. Journal of Pain Research. 2017; 10:1521-1527

171. Chia YY, Liu K, Liu YC, Chang HC, Wong CS. Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. Anesthesia and Analgesia. 1998; 86(6):1245-9

172. Cho JS, Kim HI, Lee KY, Son T, Bai SJ, Choi H et al. Comparison of the effects of patient-controlled epidural and intravenous analgesia on postoperative bowel function after laparoscopic gastrectomy: a prospective randomized study. Surgical Endoscopy. 2017; 31(11):4688-4696

173. Choi DH, Kim JA, Chung IS. Comparison of combined spinal epidural anesthesia and epidural anesthesia for cesarean section. Acta Anaesthesiologica Scandinavica. 2000; 44(2):214-219

174. Choi DH, Kim JA, Sim WS. The effects of intraoperative epidural morphine on postcesarean intravenous patient-controlled analgesia. Korean Journal of Anesthesiology. 2000; 38(1):112-117

175. Choi P, Bhandari M, Scott J, Douketis J. Epidural analgesia for pain relief following hip or knee replacement. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD003071. DOI: 10.1002/14651858.CD003071.

176. Choi SJ, Kim HK, Kim GS, Noh JH, Heo JS, Sohn TS. Effects of intravenous patient controlled analgesia with morphine, meperidine or fentanyl on bowel function after gastrectomy. Korean Journal of Anesthesiology. 2003; 45(3):347-351

177. Choi SK, Yoon MH, Choi JI, Kim WM, Heo BH, Park KS et al. Comparison of effects of intraoperative nefopam and ketamine infusion on managing postoperative pain after laparoscopic cholecystectomy administered remifentanil. Korean Journal of Anesthesiology. 2016; 69(5):480-486

178. Choi SK, Yoon SH, Lee JH, Hwang JH, Jung WS, Kim YH. Patient controlled analgesia of alfentanil after a total abdominal hysterectomy: A comparison of the intravenous and epidural route. Korean Journal of Pain. 2007; 20(2):169-173

179. Choi YS, Shim JK, Song JW, Kim JC, Yoo YC, Kwak YL. Combination of pregabalin and dexamethasone for postoperative pain and functional outcome in patients undergoing lumbar spinal surgery: a randomized placebo-controlled trial. Clinical Journal of Pain. 2013; 29(1):9-14

180. Choiniere M, Rittenhouse BE, Perreault S, Chartrand D, Rousseau P, Smith B et al. Efficacy and costs of patient-controlled analgesia versus regularly administered intramuscular opioid therapy. Anesthesiology. 1998; 89(6):1377-1388

181. Chotton T, Singh NR, Singh LC, Laithangbam PS, Singh HS. The effect of pregabalin for relief of postoperative pain after abdominal hysterectomy. Journal of Medical Society. 2015; 28(1):18-21

182. Choudhuri AH, Uppal R. A comparison between intravenous paracetamol plus fentanyl and intravenous fentanyl alone for postoperative analgesia during laparoscopic cholecystectomy. Anesthesia Essays and Researches. 2011; 5(2):196-200

183. Christensen K, Daniels S, Bandy D, Ernst CC, Hamilton DA, Mermelstein FH et al. A double-blind placebo-controlled comparison of a novel formulation of intravenous diclofenac and ketorolac for postoperative third molar extraction pain. Anesthesia Progress. 2011; 58(2):73-81

184. Chrubasik S, Chrubasik J, Pfisterer M, Hage R, Schulte-Monting J. Comparison of morphine with and without fentanyl for epidural analgesia after major abdominal surgery. Regional Anesthesia. 1996; 21(3):175-81

185. Chui PT, Gin T. A comparison between ketorolac and diclofenac in laparoscopic sterilization. European Journal of Anaesthesiology. 1995; 12(6):597-601

186. Chung HG, Kang PH, Lee KH. Comparison of postoperative analgesia and side effects of continuous epidural morphine infusion and continuous intravenous morphine infusion following cesarean section. Korean Journal of Anesthesiology. 1997; 32(1):97-103

187. Clarke H, Kay J, Mitsakakis N, Katz J. Acute pain after total hip arthroplasty does not predict the development of chronic postsurgical pain 6 months later. Journal of Anesthesia. 2010; 24(4):537-43

188. Clarke H, Kirkham KR, Orser BA, Katznelson R, Mitsakakis N, Ko R et al. Gabapentin reduces preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery: a blinded randomized placebo-controlled trial. Canadian Journal of Anaesthesia. 2013; 60(5):432-43

189. Clarke H, Pereira S, Kennedy D, Andrion J, Mitsakakis N, Gollish J et al. Adding gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty. Acta Anaesthesiologica Scandinavica. 2009; 53(8):1073-83

190. Clarke R, Derry S, Moore RA. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD004309. DOI: 10.1002/14651858.CD004309.pub3.

191. Clendenen SR, Rajendran S, Kopacz DJ, Greengrass RA, Robards CB, Weinstein DM et al. Pregabalin as an adjunct to a multimodal analgesic regimen to achieve opioid sparing in arthroscopic rotator cuff repair. Romanian Journal of Anaesthesia and Intensive Care. 2010; 17(1):5-10

192. Coe A, Sarginson R, Smith MW, Donnelly RJ, Russell GN. Pain following thoracotomy. A randomised, double-blind comparison of lumbar versus thoracic epidural fentanyl. Anaesthesia. 1991; 46(11):918-21

193. Cogan J, Lalumiere G, Vargas-Schaffer G, Deschamps A, Yegin Z. Low-dose intravenous ketamine for postcardiac surgery pain: Effect on opioid consumption and the incidence of chronic pain. Annals of Cardiac Anaesthesia. 2017; 20(4):395-398

194. Cohen BE, Hartman MB, Wade JT, Miller JS, Gilbert R, Chapman TM. Postoperative pain control after lumbar spine fusion. Patient-controlled analgesia versus continuous epidural analgesia. Spine. 1997; 22(16):1892-6; discussion 1896-7

195. Cohen S, Lowenwirt I, Pantuck CB, Amar D, Pantuck EJ. Bupivacaine 0.01% and/or epinephrine 0.5 microg/ml improve epidural fentanyl analgesia after cesarean section. Anesthesiology. 1998; 89(6):1354-61

196. Collins SL, Moore RA, McQuay HJ, Wiffen PJ. Oral ibuprofen and diclofenac in post-operative pain: a quantitative systematic review. European Journal of Pain. 1998; 2(4):285-291

197. Colombani S, Kabbani Y, Mathoulin-Pélissier S, Gékière JP, Dixmérias F, Monnin D et al. Administration of ketamine during induction and maintenance of anaesthesia in postoperative pain prevention. Annales Françaises d'Anesthésie et de Réanimation. 2008; 27(3):202-207

198. Colwell Jr CW, Morris BA. Patient-controlled analgesia compared with intramuscular injection of analgesics for the management of pain after an orthopaedic procedure. Journal of Bone and Joint Surgery - American Volume. 1995; 77(5):726-733

199. Commercial Medicines Unit (CMU), Department of Health. Electronic market information tool (EMIT). 2011. Available from: http://cmu.dh.gov.uk/electronic-market-information-tool-emit/ Last accessed: 01/09/2019

200. Concha M, Dagnino J, Cariaga M, Aguilera J, Aparicio R, Guerrero M. Analgesia after thoracotomy: epidural fentanyl/bupivacaine compared with intercostal nerve block plus intravenous morphine. Journal of Cardiothoracic and Vascular Anesthesia. 2004; 18(3):322-6

201. Cooper DW, Ryall DM, Desira WR. Extradural fentanyl for postoperative analgesia: predominant spinal or systemic action? British Journal of Anaesthesia. 1995; 74(2):184-7

202. Cooper DW, Saleh U, Taylor M, Whyte S, Ryall D, Kokri MS et al. Patient-controlled analgesia: epidural fentanyl and i.v. morphine compared after caesarean section. British Journal of Anaesthesia. 1999; 82(3):366-70

203. Cooper SA, Berrie R, Cohn P. Comparison of ketoprofen, ibuprofen, and placebo in a dental surgery pain model. Advances in Therapy. 1988; 5(3):43-53

204. Correll DJ, Viscusi ER, Grunwald Z, Moore JH, Jr. Epidural analgesia compared with intravenous morphine patient-controlled analgesia: postoperative outcome measures after mastectomy with immediate TRAM flap breast reconstruction. Regional Anesthesia and Pain Medicine. 2001; 26(5):444-9

205. Cottam DR, Fisher B, Atkinson J, Link D, Volk P, Friesen C et al. A randomized trial of bupivicaine pain pumps to eliminate the need for patient controlled analgesia pumps in primary laparoscopic Roux-en-Y gastric bypass. Obesity Surgery. 2007; 17(5):595-600

206. Cowan CM, Kendall JB, Barclay PM, Wilkes RG. Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for caesarean section under spinal anaesthesia. British Journal of Anaesthesia. 2002; 89(3):452-8

207. Crisp CC, Bandi S, Kleeman SD, Oakley SH, Vaccaro CM, Estanol MV et al. Patient-controlled versus scheduled, nurse-administered analgesia following vaginal reconstructive surgery: a randomized trial. American Journal of Obstetrics and Gynecology. 2012; 207(5):433.e1-6

208. Crousier M, Cognet V, Khaled M, Gueugniaud PY, Piriou V. Effect of ketamine on prevention of postmastectomy chronic pain. A pilot study. Annales Françaises d'Anesthésie et de Réanimation. 2008; 27(12):987-993

209. Cullen ML, Staren ED, el-Ganzouri A, Logas WG, Ivankovich AD, Economou SG. Continuous epidural infusion for analgesia after major abdominal operations: a randomized, prospective, double-blind study. Surgery. 1985; 98(4):718-28

210. Curtis GB, Johnson GH, Clark P, Taylor R, Brown J, O'Callaghan R et al. Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. European Journal of Clinical Pharmacology. 1999; 55(6):425-9

211. D'Alonzo RC, Bennett-Guerrero E, Podgoreanu M, D'Amico TA, Harpole DH, Shaw AD. A randomized, double blind, placebo controlled clinical trial of the preoperative use of ketamine for reducing inflammation and pain after thoracic surgery. Journal of Anesthesia. 2011; 25(5):672-8

212. Dahi-Taleghani M, Fazli B, Ghasemi M, Vosoughian M, Dabbagh A. Effect of intravenous patient controlled ketamine analgesiaon postoperative pain in opium abusers. Anesthesiology & Pain Medicine. 2014; 4(1):e14129

213. Dahl JB, Daugaard JJ, Kristoffersen E, Johannsen HV, Dahl JA. Perineuronal morphine: a comparison with epidural morphine. Anaesthesia. 1988; 43(6):463-5

214. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF. Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesthesia and Analgesia. 2000; 90(6):1419-22

215. Dal D, Kose A, Honca M, Akinci SB, Basgul E, Aypar U. Efficacy of prophylactic ketamine in preventing postoperative shivering. British Journal of Anaesthesia. 2005; 95(2):189-92

216. Danieli MV, Cavazzani Neto A, Herrera PA. Intra-articular bupivacaine or bupivacaine and morphine after ACL reconstruction. Acta Ortopedica Brasileira. 2012; 20(5):258-61

217. Daniels S, Melson T, Hamilton DA, Lang E, Carr DB. Analgesic efficacy and safety of a novel injectable formulation of diclofenac compared with intravenous ketorolac and placebo after orthopedic surgery: a multicenter, randomized, double-blinded, multiple-dose trial. Clinical Journal of Pain. 2013; 29(8):655-63

218. Daniels SE, Bandy DP, Christensen SE, Boice J, Losada MC, Liu H et al. Evaluation of the dose range of etoricoxib in an acute pain setting using the postoperative dental pain model. Clinical Journal of Pain. 2011; 27(1):1-8

219. Daniels SE, Grossman EH, Kuss ME, Talwalker S, Hubbard RC. A double-blind, randomized comparison of intramuscularly and intravenously administered parecoxib sodium versus ketorolac and placebo in a post-oral surgery pain model. Clinical Therapeutics. 2001; 23(7):1018-31

220. Darwish HM, Marzouk S, El Kholy G, El-Din WS. Low dose ketamine prevents acute opioid tolerance induced by remifentanil infusion. Egyptian Journal of Anaesthesia. 2005; 21(3):259-266

221. Dauri M, Faria S, Gatti A, Celidonio L, Carpenedo R, Sabato AF. Gabapentin and pregabalin for the acute post-operative pain management. A systematic-narrative review of the recent clinical evidences. Current Drug Targets. 2009; 10(8):716-33

222. Davis KM, Esposito MA, Meyer BA. Oral analgesia compared with intravenous patient-controlled analgesia for pain after cesarean delivery: a randomized controlled trial. American Journal of Obstetrics and Gynecology. 2006; 194(4):967-71

223. Dawson PJ, Libreri FC, Jones DJ, Libreri G, Bjorkstein AR, Royse CF. The efficacy of adding a continuous intravenous morphine infusion to patient-controlled analgesia (PCA) in abdominal surgery. Anaesthesia and Intensive Care. 1995; 23(4):453-8

224. de Beer Jde V, Winemaker MJ, Donnelly GA, Miceli PC, Reiz JL, Harsanyi Z et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. Canadian Journal of Surgery. 2005; 48(4):277-83

225. De Conno F, Ripamonti C, Gamba A, Prada A, Ventafridda V. Treatment of postoperative pain: comparison between administration at fixed hours and 'on demand' with intramuscular analgesics. European Journal of Surgical Oncology. 1989; 15(3):242-6

226. de Leon-Casasola OA, Parker BM, Lema MJ, Groth RI, Orsini-Fuentes J. Epidural analgesia versus intravenous patient-controlled analgesia. Differences in the postoperative course of cancer patients. Regional Anesthesia. 1994; 19(5):307-15

227. Debaecker L, Roosebeke A, Garot M, Andrieu G, Sanders V, Chalons N et al. Administration préopératoire de gabapentine et douleurs résiduelles après chirurgie thyroïdienne : une étude randomisée double aveugle contre placebo. Annales Françaises d'Anesthésie et de Réanimation. 2014; 33(Suppl 2):A147-A148

228. Della Rocca G, Coccia C, Pompei L, Costa MG, Pierconti F, Di Marco P et al. Post-thoracotomy analgesia: epidural vs intravenous morphine continuous infusion. Minerva Anestesiologica. 2002; 68(9):681-93

229. Demirel I, Ozer AB, Atilgan R, Kavak BS, Unlu S, Bayar MK et al. Comparison of patient-controlled analgesia versus continuous infusion of tramadol in post-cesarean section pain management. Journal of Obstetrics and Gynaecology Research. 2014; 40(2):392-398

230. Demirhan A, Akkaya A, Tekelioglu UY, Apuhan T, Bilgi M, Yurttas V et al. Effect of pregabalin and dexamethasone on postoperative analgesia after septoplasty. Pain Research and Treatment. 2014; 2014:850794

231. Demirhan A, Tekelioglu UY, Akkaya A, Bilgi M, Apuhan T, Karabekmez FE et al. Effect of pregabalin and dexamethasone addition to multimodal analgesia on postoperative analgesia following rhinoplasty surgery. Aesthetic Plastic Surgery. 2013; 37(6):1100-6

232. Demirkol Soyarslan O, Ozlu O, Utebey G, Er U. Comparing total intravenous anesthesia and spinalanesthesia in lumbar spinal surgery. Anestezi Dergisi. 2009; 17(4):186-190

233. Deng GF, Zheng JP, Wang S, Tian B, Zhang SG. Remifentanil combined with low-dose ketamine for postoperative analgesia of lower limb fracture: a double-blind, controlled study. Chinese Journal of Traumatology. 2009; 12(4):223-7

234. Deniz MN, Sertoz N, Erhan E, Ugur G. Effects of preoperative gabapentin on postoperative pain after radical retropubic prostatectomy. Journal of International Medical Research. 2012; 40(6):2362-9

235. Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD001548. DOI: 10.1002/14651858.CD001548.pub2.

236. Derry S, Moore R. Single dose oral aspirin for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD002067. DOI: 10.1002/14651858.CD002067.pub2.

237. Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD004233. DOI: 10.1002/14651858.CD004233.pub4.

238. Derry S, Wiffen PJ, Moore RA. Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD004768. DOI: 10.1002/14651858.CD004768.pub3.

239. Desai SN, Badiger SV, Tokur SB, Naik PA. Safety and efficacy of transdermal buprenorphine versus oral tramadol for the treatment of post-operative pain following surgery for fracture neck of femur: A prospective, randomised clinical study. Indian Journal of Anaesthesia. 2017; 61(3):225-229

240. Dhasmana S, Singh V, Pal US. The combined analgesic effect of gabapentin and transdermal fentanyl patch on acute and chronic pain after maxillary cancer surgeries. Journal of Maxillofacial and Oral Surgery. 2009; 8(1):55-9

241. Dichtwald S, Ben-Haim M, Papismedov L, Hazan S, Cattan A, Matot I. Intrathecal morphine versus intravenous opioid administration to impact postoperative analgesia in hepato-pancreatic surgery: a randomized controlled trial. Journal of Anesthesia. 2017; 31(2):237-245

242. Dierking G, Duedahl TH, Rasmussen ML, Fomsgaard JS, Moiniche S, Romsing J et al. Effects of gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind trial. Acta Anaesthesiologica Scandinavica. 2004; 48(3):322-7

243. Dieterich M, Muller-Jordan K, Stubert J, Kundt G, Wagner K, Gerber B. Pain management after cesarean: a randomized controlled trial of oxycodone versus intravenous piritramide. Archives of Gynecology and Obstetrics. 2012; 286(4):859-65

244. Dilli D, Dallar Y, Sorgui NH. Intravenous ketamine plus midazolam vs. intravenous ketamine for sedation in lumbar puncture: a randomized controlled trial. Indian Pediatrics. 2008; 45(11):899-904

245. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology. 2002; 97(3):560-4

246. Divella M, Cecconi M, Fasano N, Langiano N, Buttazzoni M, Gimigliano I et al. Pain relief after total hip replacement: oral CR oxycodone plus IV paracetamol versus epidural levobupivacaine and sufentanil. A randomized controlled trial. Minerva Anestesiologica. 2012; 78(5):534-41

247. Doleman B, Heinink TP, Read DJ, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. Anaesthesia. 2015; 70(10):1186-204

248. Dolgun H, Turkoglu E, Kertmen H, Gurer B, Yilmaz ER, Comoglu SS et al. Gabapentin versus pregabalin in relieving early post-surgical neuropathic pain in patients after lumbar disc herniation surgery: a prospective clinical trial. Neurological Research. 2014; 36(12):1080-5

249. Dong J, Li W, Wang Y. The effect of pregabalin on acute postoperative pain in patients undergoing total knee arthroplasty: A meta-analysis. International Journal of Surgery. 2016; 34:148-160

250. Dong P, Tang X, Cheng R, Wang J. Comparison of the efficacy of different analgesia treatments for total knee arthroplasty: A network meta-analysis. Clinical Journal of Pain. 2018; 34(11):1047-1060

251. Dordoni PL, Della Ventura M, Stefanelli A, Iannace E, Paparella P, Rocca B et al. Effect of ketorolac, ketoprofen and nefopam on platelet function. Anaesthesia. 1994; 49(12):1046-9

252. Doyle G, Jayawardena S, Ashraf E, Cooper SA. Efficacy and tolerability of nonprescription ibuprofen versus celecoxib for dental pain. Journal of Clinical Pharmacology. 2002; 42(8):912-919

253. Duale C, Frey C, Bolandard F, Barriere A, Schoeffler P. Epidural versus intrathecal morphine for postoperative analgesia after caesarean section. British Journal of Anaesthesia. 2003; 91(5):690-4

254. Duale C, Sibaud F, Guastella V, Vallet L, Gimbert YA, Taheri H et al. Perioperative ketamine does not prevent chronic pain after thoracotomy. European Journal of Pain. 2009; 13(5):497-505

255. Dullenkopf A, Muller R, Dillmann F, Wiedemeier P, Hegi TR, Gautschi S. An intraoperative pre-incision single dose of intravenous ketamine does not have an effect on postoperative analgesic requirements under clinical conditions. Anaesthesia and Intensive Care. 2009; 37(5):753-7

256. Duncan C, Riley B. BET 2: Low-dose ketamine for acute pain in the ED. Emergency Medicine Journal. 2016; 33(12):892-893

257. Durmus M, Kadir But A, Saricicek V, Ilksen Toprak H, Ozcan Ersoy M. The post-operative analgesic effects of a combination of gabapentin and paracetamol in patients undergoing abdominal hysterectomy: a randomized clinical trial. Acta Anaesthesiologica Scandinavica. 2007; 51(3):299-304

258. Dyer RA, Anderson BJ, Michell WL, Hall JM. Postoperative pain control with a continuous infusion of epidural sufentanil in the intensive care unit: a comparison with epidural morphine. Anesthesia and Analgesia. 1990; 71(2):130-6

259. Eaton MP, Chhibber AK, Green DR. Subarachnoid sufentanil versus lidocaine spinal anesthesia for extracorporeal shock wave lithotripsy. Regional Anesthesia. 1997; 22(6):515-520

260. Edwards JE, Oldman AD, Smith LA, Carroll D, Wiffen PJ, McQuay HJ et al. Oral aspirin in postoperative pain: a quantitative systematic review. Pain. 1999; 81(3):289-97

261. Edwards ND, Fletcher A, Cole JR, Peacock JE. Combined infusions of morphine and ketamine for postoperative pain in elderly patients. Anaesthesia. 1993; 48(2):124-7

262. Egbert AM, Lampros LL, Parks LL. Effects of patient-controlled analgesia on postoperative anxiety in elderly men. American Journal of Critical Care. 1993; 2(2):118-24

263. Eidy M, Fazel MR, Abdolrahimzadeh H, Moravveji AR, Kochaki E, Mohammadzadeh M. Effects of pregabalin and gabapentin on postoperative pain and opioid consumption after laparoscopic cholecystectomy. Korean Journal of Anesthesiology. 2017; 70(4):434-438

264. Eipe N, Penning J, Yazdi F, Mallick R, Turner L, Ahmadzai N et al. Perioperative use of pregabalin for acute pain-a systematic review and meta-analysis. Pain. 2015; 156(7):1284-300

265. Ekman EF, Wahba M, Ancona F. Analgesic efficacy of perioperative celecoxib in ambulatory arthroscopic knee surgery: a double-blind, placebo-controlled study. Arthroscopy. 2006; 22(6):635-42

266. El Sayed El-Gohary MM, Fatthallah MA. Pregabalin single dose in functional endoscopic sinus surgery analgesic and antiplatelet effect. Ain Shams Journal of Anaesthesiology. 2014; 30:93-103

267. Elia N, Tramer MR. Ketamine and postoperative pain--a quantitative systematic review of randomised trials. Pain. 2005; 113(1-2):61-70

268. Elkaradawy SA, Elbanawy HS, Mahmoud K. Silent myocardial ischaemia in diabetic patients after general anaesthesia with 24 h intravenous opioids or with epidural analgesia. Egyptian Journal of Anaesthesia. 2011; 27(4):279-286

269. Elkassem SA. Effects of low dose postoperative intravenous ketamine vs tramadol on postoperative patient controlled epidural analgesia after cruciate ligament reconstruction surgery. Egyptian Journal of Anaesthesia. 2008; 24(2):119-128

270. Elliott TD, Yablonki MJ, Dosch M, Aston R. A comparison of the effects of preoperative ibuprofen, intraoperative ketorolac and intraoperative fentanyl on postoperative pain in the ambulatory surgery patient following gynecological laparoscopy. Journal of the American Association of Nurse Anesthetists. 1993; 61(4):428-429

271. Ellis DJ, Millar WL, Reisner LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. Anesthesiology. 1990; 72(6):981-6

272. Eman A, Bilir A, Beyaz SG. The effects of preoperative pregabalin on postoperative analgesia and morphine consumption after abdominal hysterectomy. Acta Medica Mediterranea. 2014; 30(2):481-485

273. Emir E, Serin S, Erbay RH, Sungurtekin H, Tomatir E. Tramadol versus low dose tramadol-paracetamol for patient controlled analgesia during spinal vertebral surgery. Kaohsiung Journal of Medical Sciences. 2010; 26(6):308-15

274. Endoh M, Matsuda A. Epidural administration of buprenorphine after combined spinal epidural anesthesia. Japanese Journal of Anesthesiology. 1996; 45(11):1396-1399

275. Engelman E, Cateloy F. Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized-controlled trials. Acta Anaesthesiologica Scandinavica. 2011; 55(8):927-43

276. Ercan S, Akpek E, Aslim E, Akay H, Donmez A. The effects of gabapentin on intraoperative cooperation, stress response and postoperative analgesia in patients undergoing carotid endartectomy with regional anesthesia. Journal of Cardio-Vascular-Thoracic Anaesthesia and Intensive Care Society. 2014; 20:7-15

277. Eriksson-Mjoberg M, Svensson JO, Almkvist O, Olund A, Gustafsson LL. Extradural morphine gives better pain relief than patient-controlled i.v. morphine after hysterectomy. British Journal of Anaesthesia. 1997; 78(1):10-6

278. Eroglu A. A comparison of patient-controlled subacromial and i.v. analgesia after open acromioplasty surgery. British Journal of Anaesthesia. 2006; 96(4):497-501

279. Eskandar AM, Ebeid AM. Effect of pregabalin on postoperative pain after shoulder arthroscopy. Egyptian Journal of Anaesthesia. 2013; 29(4):363-367

280. Eskander WF, Harvey PB, Kestin IG. Subarachnoid diamorphine compared with extradural diamorphine for postoperative pain relief following elective caesarean section. International Journal of Obstetric Anesthesia. 1994; 3(3):173

281. Essex MN, Choi HY, Bhadra Brown P, Cheung R. A randomized study of the efficacy and safety of parecoxib for the treatment of pain following total knee arthroplasty in Korean patients. Journal of Pain Research. 2018; 11:427-433

282. Essving P, Axelsson K, Aberg E, Spannar H, Gupta A, Lundin A. Local infiltration analgesia versus intrathecal morphine for postoperative pain management after total knee arthroplasty: a randomized controlled trial. Anesthesia and Analgesia. 2011; 113(4):926-33

283. Estanon-Garcia I, Lopez-Jimenez FA. Comparison between intrathecal morphine at high doses vs low doses in spinal lumbo-sacral surgery for postoperative control pain. Revista Mexicana de Anestesiologia. 2008; 31(2):93-100

284. Esteller-Martinez V, Paredes-Garcia J, Valmaseda-Castellon E, Berini-Aytes L, Gay-Escoda C. Analgesic efficacy of diclofenac sodium versus ibuprofen following surgical extraction of impacted lower third molars. Medicina Oral, Patología Oral y Cirugía Bucal. 2004; 9(5):448-53; 444-8

285. Fabritius ML, Geisler A, Petersen PL, Nikolajsen L, Hansen MS, Kontinen V et al. Gabapentin for post-operative pain management - a systematic review with meta-analyses and trial sequential analyses. Acta Anaesthesiologica Scandinavica. 2016; 60(9):1188-208

286. Fabritius ML, Strom C, Koyuncu S, Jaeger P, Petersen PL, Geisler A et al. Benefit and harm of pregabalin in acute pain treatment: a systematic review with meta-analyses and trial sequential analyses. British Journal of Anaesthesia. 2017; 119(4):775-791

287. Facchinetti F, Casini ML, Costabile L, Malavasi B, Unfer V. Diclofenac pyrrolidine versus Ketoprofen for the relief of pain from episiotomy: a randomized controlled trial. Acta Obstetricia et Gynecologica Scandinavica. 2005; 84(10):951-5

288. Fanshawe MP. A comparison of patient controlled epidural pethidine versus single dose epidural morphine for analgesia after caesarean section. Anaesthesia and Intensive Care. 1999; 27(6):610-4

289. Fant F, Axelsson K, Sandblom D, Magnuson A, Andersson SO, Gupta A. Thoracic epidural analgesia or patient-controlled local analgesia for radical retropubic prostatectomy: a randomized, double-blind study. British Journal of Anaesthesia. 2011; 107(5):782-9

290. Fassoulaki A, Chassiakos D, Melemeni A. Intermittent epidural vs continuous wound infusion of ropivacaine for acute and chronic pain control after hysterectomy or myomectomy: a randomized controlled trial. Pain Medicine. 2014; 15(9):1603-8

291. Fatthallah M, Elquesny K, Abdelmageed W, Elsayed M. Preemptive single oral dose of gabapentin (600 mg) provides safe adequate analgesia for immediate post-tonsillectomy pain. Ain Shams Journal of Anesthesiology. 2012; 5(1):145-55

292. Fayed NA, Abo El-Wafa HB, Gab-Alla NM, Yassen KA, Lotfy ME. Comparison between intravenous patient controlled analgesia and patient controlled epidural analgesia in cirrhotic patients after hepatic resection. Middle East Journal of Anesthesiology. 2014; 22(5):467-76

293. Fenlon S, Collyer J, Giles J, Bidd H, Lees M, Nicholson J et al. Oral vs intravenous paracetamol for lower third molar extractions under general anaesthesia: is oral administration inferior? British Journal of Anaesthesia. 2013; 110(3):432-7

294. Fineschi G, Tamburrelli FC, Francucci BM, Pisati R. Oral diclofenac dispersible provides a faster onset of analgesia than intramuscular ketorolac in the treatment of postoperative pain. Clinical Drug Investigation. 1997; 13(1):1-7

295. Fiorelli A, Mazzella A, Passavanti B, Sansone P, Chiodini P, Iannotti M et al. Is pre-emptive administration of ketamine a significant adjunction to intravenous morphine analgesia for controlling postoperative pain? A randomized, double-blind, placebo-controlled clinical trial. Interactive Cardiovascular and Thoracic Surgery. 2015; 21(3):284-90

296. Fischer RL, Lubenow TR, Liceaga A, McCarthy RJ, Ivankovich AD. Comparison of continuous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of postoperative pain. Anesthesia and Analgesia. 1988; 67(6):559-63

297. Flacke JW, Bloor BC, Kripke BJ, Flacke WE, Warneck CM, Van Etten AP et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesthesia and Analgesia. 1985; 64(9):897-910

298. Flory DA, Fankhauser RA, McShane MA. Postoperative pain control in total joint arthroplasty: a prospective, randomized study of a fixed-dose, around-the-clock, oral regimen. Orthopedics. 2001; 24(3):243-6

299. Forbes JA, Beaver WT, Jones KF, Edquist IA, Gongloff CM, Smith WK et al. Analgesic efficacy of bromfenac, ibuprofen, and aspirin in postoperative oral surgery pain. Clinical Pharmacology and Therapeutics. 1992; 51(3):343-52

300. Forbes JA, Edquist IA, Smith FG, Schwartz MK, Beaver WT. Evaluation of bromfenac, aspirin, and ibuprofen in postoperative oral surgery pain. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 1991; 11(1):64-70

301. Forget P, Cata J. Stable anesthesia with alternative to opioids: Are ketamine and magnesium helpful in stabilizing hemodynamics during surgery? A systematic review and meta-analyses of randomized controlled trials. Best Practice & Research Clinical Anaesthesiology. 2017; 31(4):523-531

302. Forrest JB, Camu F, Greer IA, Kehlet H, Abdalla M, Bonnet F et al. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. British Journal of Anaesthesia. 2002; 88(2):227-33

303. Foss NB, Kristensen MT, Kristensen BB, Jensen PS, Kehlet H. Effect of postoperative epidural analgesia on rehabilitation and pain after hip fracture surgery: a randomized, double-blind, placebo-controlled trial. Anesthesiology. 2005; 102(6):1197-204

304. Frame JW, Rout PG. A comparison of the analgesic efficacy of flurbiprofen, diclofenac, dihydrocodeine/paracetamol and placebo following oral surgery. British Journal of Clinical Practice. 1986; 40(11):463-7

305. Fredman B, Olsfanger D, Jedeikin R. A comparative study of ketorolac and diclofenac on post-laparoscopic cholecystectomy pain. European Journal of Anaesthesiology. 1995; 12(5):501-4

306. Freedman BM, O'Hara E. Pregabalin has opioid-sparing effects following augmentation mammaplasty. Aesthetic Surgery Journal. 2008; 28(4):421-4

307. Freire GM, Cavalcante RN, Motta-Leal-Filho JM, Messina M, Galastri FL, Affonso BB et al. Controlled-release oxycodone improves pain management after uterine artery embolisation for symptomatic fibroids. Clinical Radiology. 2017; 72(5):428.e1-428.e5

308. Fricke JR, Halladay SC, Francisco CA. Efficacy and safety of naproxen sodium and ibuprofen for pain relief after oral surgery. Current Therapeutic Research - Clinical and Experimental. 1993; 54(6):619-627

309. Frouzanfard F, Fazel MR, Abolhasani A, Fakharian E, Mousavi G, Moravveji A. Effects of gabapentin on pain and opioid consumption after abdominal hysterectomy. Pain Research & Management. 2013; 18(2):94-6

310. Furuya A, Matsukawa T, Ozaki M, Nishiyama T, Kume M, Kumazawa T. Intravenous ketamine attenuates arterial pressure changes during the induction of anaesthesia with propofol. European Journal of Anaesthesiology. 2001; 18(2):88-92

311. Galinski M, Dolveck F, Combes X, Limoges V, Smail N, Pommier V et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. American Journal of Emergency Medicine. 2007; 25(4):385-90

312. Galinski SF, Pereira JA, Maestre Y, Frances S, Escolano F, Puig MM. The combination of intravenous dexamethasone and ketamine does not improve postoperative analgesia when compared to each drug individually. Pain Clinic. 2007; 19(5):223-229

313. Gallardo F, Lobo R, Pino M, Martino LE. Double blind evaluation of naproxen and ibuprofen in oral surgery outpatients. IRCS Medical Science. 1981; 9(5):440-441

314. Gallardo F, Rossi E. Double-blind evaluation of naproxen and ibuprofen in periodontal surgery. Pharmacology and Therapeutics in Dentistry. 1980; 5(3-4):69-72

315. Gan TJ, Daniels SE, Singla N, Hamilton DA, Carr DB. A novel injectable formulation of diclofenac compared with intravenous ketorolac or placebo for acute moderate-to-severe pain after abdominal or pelvic surgery: a multicenter, double-blind, randomized, multiple-dose study. Anesthesia and Analgesia. 2012; 115(5):1212-20

316. Gan TJ, Singla N, Daniels SE, Hamilton DA, Lacouture PG, Reyes CR et al. Postoperative opioid sparing with injectable hydroxypropyl-beta-cyclodextrin-diclofenac: pooled analysis of data from two Phase III clinical trials. Journal of Pain Research. 2017; 10:15-29

317. Gan TJ, Singla N, Daniels SE, Lacouture PG, Min LH, Reyes CR et al. Cardiovascular safety of hydroxypropyl-beta-cyclodextrin-diclofenac in the management of acute postsurgical pain: a pooled analysis of 2 randomized, double-blind, placebo- and active comparator-controlled phase III clinical trials. Journal of Clinical Anesthesia. 2016; 31:249-58

318. Ganne O, Abisseror M, Menault P, Malhiere S, Chambost V, Charpiat B et al. Low-dose ketamine failed to spare morphine after a remifentanil-based anaesthesia for ear, nose and throat surgery. European Journal of Anaesthesiology. 2005; 22(6):426-30

319. Garcia-Henares JF, Moral-Munoz JA, Salazar A, Del Pozo E. Effects of ketamine on postoperative pain after remifentanil-based anesthesia for major and minor surgery in adults: A systematic review and meta-analysis. Frontiers in Pharmacology. 2018; 9:921

320. Garg N, Panda NB, Gandhi KA, Bhagat H, Batra YK, Grover VK et al. Comparison of small dose ketamine and dexmedetomidine infusion for postoperative analgesia in spine surgery--a prospective randomized double-blind placebo controlled study. Journal of Neurosurgical Anesthesiology. 2016; 28(1):27-31

321. Gaskell H, Derry S, Wiffen PJ, Moore RA. Single dose oral ketoprofen or dexketoprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD007355. DOI: 10.1002/14651858.CD007355.pub3.

322. Gazal G, Al-Samadani KH. Comparison of paracetamol, ibuprofen, and diclofenac potassium for pain relief following dental extractions and deep cavity preparations. Saudi Medical Journal. 2017; 38(3):284-291

323. Geller E, Chrubasik J, Graf R, Chrubasik S, Schulte-Monting J. A randomized double-blind comparison of epidural sufentanil versus intravenous sufentanil or epidural fentanyl analgesia after major abdominal surgery. Anesthesia and Analgesia. 1993; 76(6):1243-50

324. George KA, Wright PM, Chisakuta AM, Rao NV. Thoracic epidural analgesia compared with patient controlled intravenous morphine after upper abdominal surgery. Acta Anaesthesiologica Scandinavica. 1994; 38(8):808-12

325. Ghafari M, Akrami M, Nouraishahi B, Sadegh A. Preoperative gabapentin or clonidine decreases postoperative pain and morphine consumption after abdominal hysterectomy. Research Journal of Biological Sciences. 2009; 4(4):458-463

326. Ghai A, Gupta M, Hooda S, Singla D, Wadhera R. A randomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. Saudi Journal of Anaesthesia. 2011; 5(3):252-7

327. Ghazi-Saidi K, Hajipour A. Effects of preemptive ketamine on post caesarean analgesic requirement. Acta Medica Iranica. 2002; 40(2):100-3

328. Ghee CD, Fortes DL, Liu C, Khandhar SJ. A randomized controlled trial of continuous subpleural bupivacaine after thoracoscopic surgery. Seminars in Thoracic and Cardiovascular Surgery. 2018; 30(2):240-249

329. Gherghina V, Nicolae G, Cindea I, Balcan A, Cosofret M, Sirbu V. Efficacy and adverse effects of intravenous vs epidural patientcontrolled analgesia in the elderly patients after major abdominal surgery. Romanian Journal of Anaesthesia and Intensive Care. 2010; 17(2):103-109

330. Ghoneim AA, Hegazy MM. The analgesic effect of preoperative pregabalin in radical cystectomy for cancer bladder patients. Chinese-German Journal of Clinical Oncology. 2013; 12(3):113-117

331. Gillies A, Lindholm D, Angliss M, Orr A. The use of ketamine as rescue analgesia in the recovery room following morphine administration--a double-blind randomised controlled trial in postoperative patients. Anaesthesia and Intensive Care. 2007; 35(2):199-203

332. Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Current Opinion in Anaesthesiology. 2007; 20(5):456-472

333. Gilron I, Orr E, Tu D, O'Neill JP, Zamora JE, Bell AC. A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. Pain. 2005; 113(1-2):191-200

334. Gimbel JS, Brugger A, Zhao W, Verburg KM, Geis GS. Efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. Clinical Therapeutics. 2001; 23(2):228-41

335. Ginsberg B, Sinatra RS, Adler LJ, Crews JC, Hord AH, Laurito CE et al. Conversion to oral controlled-release oxycodone from intravenous opioid analgesic in the postoperative setting. Pain Medicine. 2003; 4(1):31-38

336. Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff B. The anxiolytic effect of pregabalin in outpatients undergoing minor orthopaedic surgery. Journal of Psychopharmacology. 2011; 25(2):249-53

337. Gong Z, Ye T, Yu G, Qing X. Comparison of patient-controlled analgesia with tramadol vs morphine in patients undergoing abdominal gynecological surgery. Chinese Medical Sciences Journal. 2003; 18(3):180-184

338. Gonul O, Satilmis T, Ciftci A, Sipahi A, Garip H, Goker K. Comparison of the effects of topical ketamine and tramadol on postoperative pain after mandibular molar extraction. Journal of Oral and Maxillofacial Surgery. 2015; 73(11):2103-2107

339. Gopinathan C, Sockalingham I, Fung MA, Peat S, Hanna MH. A comparative study of patient-controlled epidural diamorphine, subcutaneous diamorphine and an epidural diamorphine/bupivacaine combination for postoperative pain. European Journal of Anaesthesiology. 2000; 17(3):189-96

340. Gousheh SM, Nesioonpour S, Javaher Foroosh F, Akhondzadeh R, Sahafi SA, Alizadeh Z. Intravenous paracetamol for postoperative analgesia in laparoscopic cholecystectomy. Anesthesiology & Pain Medicine. 2013; 3(1):214-8

341. Goyal R, Hasnain S, Mittal S, Shreevastava S. A randomized, controlled trial to compare the efficacy and safety profile of a dexmedetomidine-ketamine combination with a propofol-fentanyl combination for ERCP. Gastrointestinal Endoscopy. 2016; 83(5):928-33

342. Grace RF, Lesteour T, Sala T, Stewart J. A randomized comparison of low-dose ketamine and lignocaine infiltration with ketamine-diazepam anaesthesia for post partum tubal ligation in Vanuatu. Anaesthesia and Intensive Care. 2001; 29(1):30-3

343. Grady MV, Mascha E, Sessler DI, Kurz A. The effect of perioperative intravenous lidocaine and ketamine on recovery after abdominal hysterectomy. Anesthesia and Analgesia. 2012; 115(5):1078-84

344. Graf G, Jelen M, Jamnig D, Schabus H, Pipam W, Likar R. A comparison of the efficacy and rate of side-effects of mefenamic acid and naproxen in adult patients following elective tonsillectomy: A randomized double-blind study. Acute Pain. 2008; 10(3-4):131-136

345. Graham D, Russell I. Double-blind study to assess the analgesic sparing effect of 0.3 mg diamorphine given intrathecally at elective caesarean section. International Journal of Obstetric Anesthesia. 1995; 4(3):179-180

346. Graham D, Russell IF. A double-blind assessment of the analgesic sparing effect of intrathecal diamorphine (0.3 mg) with spinal anaesthesia for elective caesarean section. International Journal of Obstetric Anesthesia. 1997; 6(4):224-30

347. Grant GJ, Zakowski M, Ramanathan S, Boyd A, Turndorf H. Thoracic versus lumbar administration of epidural morphine for postoperative analgesia after thoracotomy. Regional Anesthesia. 1993; 18(6):351-5

348. Grant RP, Dolman JF, Harper JA, White SA, Parsons DG, Evans KG et al. Patient controlled lumbar epidural fentanyl for post thoracotomy pain. Canadian Journal of Anaesthesia. 1990; 37(4 Pt 2):S45

349. Green RJ, Chambers J, Thomas PW, Monnery L, Titley G, Doyle T. Comparison of the relative analgesic efficacies of epidural or intramuscular diamorphine following total knee arthroplasty. European Journal of Anaesthesiology. 2007; 24(11):951-7

350. Grover VK, Mathew PJ, Yaddanapudi S, Sehgal S. A single dose of preoperative gabapentin for pain reduction and requirement of morphine after total mastectomy and axillary dissection: randomized placebo-controlled double-blind trial. Journal of Postgraduate Medicine. 2009; 55(4):257-60

351. Guay J, Kopp S. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD005059. DOI: 10.1002/14651858.CD005059.pub4.

352. Guignard B, Coste C, Costes H, Sessler DI, Lebrault C, Morris W et al. Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. Anesthesia and Analgesia. 2002; 95(1):103-8

353. Guillou N, Tanguy M, Seguin P, Branger B, Campion JP, Malledant Y. The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. Anesthesia and Analgesia. 2003; 97(3):843-7

354. Guinard JP, Mavrocordatos P, Chiolero R, Carpenter RL. A randomized comparison of intravenous versus lumbar and thoracic epidural fentanyl for analgesia after thoracotomy. Anesthesiology. 1992; 77(6):1108-15

355. Gulucu C, Yilmaz AA, Yalcin S, Can OS, Demiralp S, Alkis N. The effects of patient controlled analgesia methods with intravenous and epidural morphine on cognitive functions in geriatric patients. Anestezi Dergisi. 2009; 17(1):41-48

356. Gunjan, Kohli M, Singh PK, Gupta R, Chaudhary AK, Kumar V et al. Multimodal versus conventional approach for postoperative pain relief in oral cancer patients. Journal of Clinical and Diagnostic Research. 2016; 10(1):UC05-UC08

357. Gupta A, Axelsson K, Thorn SE, Matthiessen P, Larsson LG, Holmstrom B et al. Low-dose bupivacaine plus fentanyl for spinal anesthesia during ambulatory inguinal herniorrhaphy: a comparison between 6 mg and 7. 5 mg of bupivacaine. Acta Anaesthesiologica Scandinavica. 2003; 47(1):13-9

358. Gupta A, Fant F, Axelsson K, Sandblom D, Rykowski J, Johansson JE et al. Postoperative analgesia after radical retropubic prostatectomy: a double-blind comparison between low thoracic epidural and patient-controlled intravenous analgesia. Anesthesiology. 2006; 105(4):784-93

359. Gupta K, Mitra S, Kazal S, Saroa R, Ahuja V, Goel P. I.V. paracetamol as an adjunct to patient-controlled epidural analgesia with levobupivacaine and fentanyl in labour: a randomized controlled study. British Journal of Anaesthesia. 2016; 117(5):617-622

360. Gupta VP, Dhaliwal U, Prasad N. Ketorolac tromethamine in the maintenance of intraoperative mydriasis. Ophthalmic Surgery and Lasers. 1997; 28(9):731-8

361. Gurlit S, Reinhardt S, Mollmann M. Continuous spinal analgesia or opioid-added continuous epidural analgesia for postoperative pain control after hip replacement. European Journal of Anaesthesiology. 2004; 21(9):708-14

362. Gurnani A, Sharma PK, Rautela RS, Bhattacharya A. Analgesia for acute musculoskeletal trauma: low-dose subcutaneous infusion of ketamine. Anaesthesia and Intensive Care. 1996; 24(1):32-6

363. Gurunathan U, Rapchuk IL, King G, Barnett AG, Fraser JF. The effect of pregabalin and celecoxib on the analgesic requirements after laparoscopic cholecystectomy: a randomized controlled trial. Journal of Anesthesia. 2016; 30(1):64-71

364. Hadhimane A, Shankariah M, Neswi KV. Pre-emptive analgesia with ketamine for relief of postoperative pain after surgical removal of impacted mandibular third molars. Journal of Maxillofacial and Oral Surgery. 2016; 15(2):156-163

365. Hadi BA, Al Daas R, Ramadani R, Naylor I, Zelko R, Saleh M. The influence of anaesthetic drug selection for scoliosis surgery on the management of intraoperative haemodynamic stability and postoperative pain - Pharmaceutical care programme. Southern African Journal of Anaesthesia and Analgesia. 2009; 15(5):10-14

366. Hadi BA, Al Ramadani R, Daas R, Naylor I, Zelko R. Remifentanil in combination with ketamine versus remifentanil in spinal fusion surgery--a double blind study. International Journal of Clinical Pharmacology and Therapeutics. 2010; 48(8):542-8

367. Hadi BA, Daas R, Zelko R. A randomized, controlled trial of a clinical pharmacist intervention in microdiscectomy surgery - Low dose intravenous ketamine as an adjunct to standard therapy. Saudi Pharmaceutical Journal. 2013; 21(2):169-75

368. Hah J, Mackey SC, Schmidt P, McCue R, Humphreys K, Trafton J et al. Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort: a randomized clinical trial. JAMA Surgery. 2018; 153(4):303-311

369. Hakan Erbay R, Ermumcu O, Hanci V, Atalay H. A comparison of spinal anesthesia with low-dose hyperbaric levobupivacaine and hyperbaric bupivacaine for transurethral surgery: a randomized controlled trial. Minerva Anestesiologica. 2010; 76(12):992-1001

370. Hakobyan RV, Mkhoyan GG. Epidural analgesia decreases intraabdominal pressure in postoperative patients with primary intra-abdominal hypertension. Acta Clinica Belgica. 2008; 63(2):86-92

371. Haliloglu M, Ozdemir M, Uzture N, Cenksoy PO, Bakan N. Perioperative low-dose ketamine improves postoperative analgesia following cesarean delivery with general anesthesia. Journal of Maternal-Fetal & Neonatal Medicine. 2016; 29(6):962-966

372. Hallworth SP, Bell R, Fernando R, Parry MG, Lim GH. A comparison of intrathecal and epidural diamorphine for postoperative pain relief following elective caesarean section. International Journal of Obstetric Anesthesia. 1997; 6:199

373. Hamilton TW, Strickland LH, Pandit HG. A meta-analysis on the use of gabapentinoids for the treatment of acute postoperative pain following total knee arthroplasty. Journal of Bone & Joint Surgery - American Volume. 2016; 98(16):1340-50

374. Han C, Kuang MJ, Ma JX, Ma XL. Is pregabalin effective and safe in total knee arthroplasty? A PRISMA-compliant meta-analysis of randomized-controlled trials. Medicine. 2017; 96(26):e6947

375. Han C, Li XD, Jiang HQ, Ma JX, Ma XL. The use of gabapentin in the management of postoperative pain after total hip arthroplasty: a meta-analysis of randomised controlled trials. Journal of Orthopaedic Surgery. 2016; 11(1):79

376. Han JS, Park SK, Suh MS, Yoo ES, Lee SY, Min BH. Effects of intravenous and epidural patient-controlled analgesia on postoperative pain and knee rehabilitation after a unilateral total knee replacement. Korean Journal of Anesthesiology. 2001; 40(1):47-53

377. Han SY, Jin HC, Yang WD, Lee JH, Cho SH, Chae WS et al. The effect of low-dose ketamine on post-caesarean delivery analgesia after spinal anesthesia. Korean Journal of Pain. 2013; 26(3):270-6

378. Hancke E, Lampinski M, Suchan K, Völke K. Pain management after hemorrhoidectomy. Patient-controlled analgesia vs conventional pain therapy. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen. 2013; 84(7):587-593

379. Hanna M, Moon JY. A review of dexketoprofen trometamol in acute pain. Current Medical Research and Opinion. 2019; 35(2):189-202

380. Hanoura S, Sharaa M, Refaie M, Singh R. A comparative study of preemptive effect of pregabalin and gabapentin on postoperative pain after coronary artery bypass graft surgery: A clinical randomized trial. Journal of the Egyptian Society of Cardio-Thoracic Surgery. 2018; 26(4):245-251

381. Hansdottir V, Philip J, Olsen MF, Eduard C, Houltz E, Ricksten SE. Thoracic epidural versus intravenous patient-controlled analgesia after cardiac surgery: a randomized controlled trial on length of hospital stay and patient-perceived quality of recovery. Anesthesiology. 2006; 104(1):142-51

382. Hanzawa A, Handa T, Kohkita Y, Ichinohe T, Fukuda KI. A comparative study of oral analgesics for postoperative pain after minor oral surgery. Anesthesia Progress. 2018; 65(1):24-29

383. Harukuni I, Yamaguchi H, Sato S, Naito H. The comparison of epidural fentanyl, epidural lidocaine, and intravenous fentanyl in patients undergoing gastrectomy. Anesthesia and Analgesia. 1995; 81(6):1169-74

384. Hasanein R, El-Sayed W, Nabil N, Elsayed G. The effect of combined remifentanil and low dose ketamine infusion in patients undergoing laparoscopic gastric bypass. Egyptian Journal of Anaesthesia. 2011; 27(4):255-260

385. Hassani V, Pazouki A, Nikoubakht N, Chaichian S, Sayarifard A, Shakib Khankandi A. The effect of gabapentin on reducing pain after laparoscopic gastric bypass surgery in patients with morbid obesity: a randomized clinical trial. Anesthesiology & Pain Medicine. 2015; 5(1):e22372

386. Hausken J, Fretland AA, Edwin B, Andersen MH, Dagenborg VJ, Bjornelv GMW et al. Intravenous patient-controlled analgesia versus thoracic epidural analgesia after open liver surgery: A prospective, randomized, controlled, noninferiority trial. Annals of Surgery. 2019; 270(2):193-199

387. Hayes C, Armstrong-Brown A, Burstal R. Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: a randomized, controlled trial. Anaesthesia and Intensive Care. 2004; 32(3):330-8

388. Hecker BR, Albert L. Patient-controlled analgesia: a randomized, prospective comparison between two commercially available PCA pumps and conventional analgesic therapy for postoperative pain. Pain. 1988; 35(1):115-20

389. Heesen M, Bohmer J, Brinck EC, Kontinen VK, Klohr S, Rossaint R et al. Intravenous ketamine during spinal and general anaesthesia for caesarean section: systematic review and meta-analysis. Acta Anaesthesiologica Scandinavica. 2015; 59(4):414-26

390. Hegarty DA, Shorten GD. A randomised, placebo-controlled trial of the effects of preoperative pregabalin on pain intensity and opioid consumption following lumbar discectomy. Korean Journal of Pain. 2011; 24(1):22-30

391. Hege-Scheuing G, Michaelsen K, Bühler A, Kustermann J, Seeling W. Analgesia with intra-articular morphine following knee joint arthroscopy? A double-blind, randomized study with patient-controlled analgesia. Der Anaesthesist. 1995; 44(5):351-358

392. Heidari-Tabaee-Zavare SM, Qanavi M, Raeesi L. Comparing the preventive effect of combination of ketamine with metoclopramide or fentanyl on the postoperative pain after laparoscopic cholecystectomy under general anesthesia. Journal of Isfahan Medical School. 2015; 33(347):1357-1369

393. Heidari SM, Khalili G, Roohani S, Koushki AM. Comparing the effects of ketamine alone and in combination with metoclopramide on postoperative pain. Journal of Isfahan Medical School. 2013; 30(211):2441-2449

394. Hercock T, Gillham MJ, Sleigh J, Jones SF. The addition of ketamine to patient controlled morphine analgesia does not improve quality of analgesia after total abdominal hysterectomy. Acute Pain. 1999; 2(2):68-72

395. Hering R, Schumacher T, Müller H. Postoperative peridural analgesia. Continuous versus patient-controlled administration of a low-dose mixture of sufentanil, clonidine and bupivacaine. Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie. 1997; 32(11):659-664

396. Hetta DF, Mohamed MA, Mohammad MF. Analgesic efficacy of pregabalin in acute postmastectomy pain: placebo controlled dose ranging study. Journal of Clinical Anesthesia. 2016; 34:303-9

397. Higgins MS, Givogre JL, Marco AP, Blumenthal PD, Furman WR. Recovery from outpatient laparoscopic tubal ligation is not improved by preoperative administration of ketorolac or ibuprofen. Anesthesia and Analgesia. 1994; 79(2):274-80

398. Himmelseher S, Ziegler-Pithamitsis D, Argiriadou H, Martin J, Jelen-Esselborn S, Kochs E. Small-dose S(+)-ketamine reduces postoperative pain when applied with ropivacaine in epidural anesthesia for total knee arthroplasty. Anesthesia and Analgesia. 2001; 92(5):1290-5

399. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain--a systematic review of randomized controlled trials. Pain. 2006; 126(1-3):91-101

400. Ho KY, Huh BK, White WD, Yeh CC, Miller EJ. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. Clinical Journal of Pain. 2008; 24(1):51-5

401. Ho ST, Wang JJ, Liu HS, Hu OY, Tzeng JI, Liaw WJ. Comparison of PCA nalbuphine and morphine in Chinese gynecologic patients. Acta Anaesthesiologica Sinica. 1998; 36(2):65-70

402. Holmstrom B, Laugaland K, Rawal N, Hallberg S. Combined spinal epidural block versus spinal and epidural block for orthopaedic surgery. Canadian Journal of Anaesthesia. 1993; 40(7):601-6

403. Hong BH, Lee WY, Kim YH, Yoon SH, Lee WH. Effects of intraoperative low dose ketamine on remifentanil-induced hyperalgesia in gynecologic surgery with sevoflurane anesthesia. Korean Journal of Anesthesiology. 2011; 61(3):238-43

404. Hong JY, Lee YW. The effects of preoperative or postperitoneal closure epidural ketamine on epidural anesthesia and analgesia for obstetric patients. Korean Journal of Anesthesiology. 1999; 37(2):276-281

405. Hopkins D, Shipton EA, Potgieter D, Van derMerwe CA, Boon J, De Wet C et al. Comparison of tramadol and morphine via subcutaneous PCA following major orthopaedic surgery. Canadian Journal of Anaesthesia. 1998; 45(5 Pt 1):435-42

406. Hosseini VS, Yekta RA, Marashi S, Marashi SM. The efficacy of melatonin, clonidine and gabapentin in reducing preoperative anxiety and postoperative pain in patients undergoing laparoscopic cholecystectomy: A randomized clinical trial. Archives of Anesthesiology and Critical Care. 2015; 1(4):120-125

407. Hotta K, Endo T, Taira K, Sata N, Inoue S, Takeuchi M et al. Comparison of the analgesic effects of continuous extrapleural block and continuous epidural block after video-assisted thoracoscopic surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2011; 25(6):1009-13

408. Houmes RJ, Voets MA, Verkaaik A, Erdmann W, Lachmann B. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesthesia and Analgesia. 1992; 74(4):510-4

409. Howell PR, Gambling DR, Pavy T, McMorland G, Douglas MJ. Patient-controlled analgesia following caesarean section under general anaesthesia: a comparison of fentanyl with morphine. Canadian Journal of Anaesthesia. 1995; 42(1):41-5

410. Hu DH, Li YL, Cai MX, Zhang H, Xiang MF, Shuai B et al. Epidural butorphanol analgesia in elderly patients undergoing hip replacement. Journal of Southern Medical University. 2009; 29(7):1435-1437

411. Hu J, Huang D, Li M, Wu C, Zhang J. Effects of a single dose of preoperative pregabalin and gabapentin for acute postoperative pain: a network meta-analysis of randomized controlled trials. Journal of Pain Research. 2018; 11:2633-2643

412. Hu J, Liao Q, Zhang F, Tong J, Ouyang W. Chronic postthoracotomy pain and perioperative ketamine infusion. Journal of Pain & Palliative Care Pharmacotherapy. 2014; 28(2):117-121

413. Huang FY, Fan SZ, Wang MS, Chen TL, Sun WZ, Lin SY. Comparison of continuous epidural infusion of fentanyl and fentanyl-bupivacaine for post cholecystectomy pain control. Anaesthesiologica Sinica. 1990; 28(1):9-13

414. Hubner M, Blanc C, Roulin D, Winiker M, Gander S, Demartines N. Randomized clinical trial on epidural versus patient-controlled analgesia for laparoscopic colorectal surgery within an enhanced recovery pathway. Annals of Surgery. 2015; 261(4):648-53

415. Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled intravenous opioid analgesia versus conventional opioid analgesia for postoperative pain control: A quantitative systematic review. Acute Pain. 2005; 7(3):115-132

416. Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD003348. DOI: 10.1002/14651858.CD003348.pub2.

417. Huot MP, Chouinard P, Girard F, Ruel M, Lafontaine ER, Ferraro P. Gabapentin does not reduce post-thoracotomy shoulder pain: a randomized, double-blind placebo-controlled study. Canadian Journal of Anaesthesia. 2008; 55(6):337-43

418. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Regional Anesthesia and Pain Medicine. 2006; 31(3):237-47

419. Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after caesarean section under spinal anaesthesia. British Journal of Anaesthesia. 1998; 81(2):135-9

420. Husegaard HC, Petersen TK, Rybro L, Schurizek BA, Wernberg M. Treatment of postoperative pain with epidural buprenorphine and morphine after high laparotomies. Ugeskrift for Laeger. 1984; 146(1):14-17

421. Hutchins JL, Grandelis AJ, Kaizer AM, Jensen EH. Thoracic paravertebral block versus thoracic epidural analgesia for post-operative pain control in open pancreatic surgery: A randomized controlled trial. Journal of Clinical Anesthesia. 2018; 48:41-45

422. Hwang BY, Kwon JY, Kim E, Lee DW, Kim TK, Kim HK. Oxycodone vs. fentanyl patient-controlled analgesia after laparoscopic cholecystectomy. International Journal of Medical Sciences. 2014; 11(7):658-62

423. Hwang JK, Lee SJ, Kil HY, Lee SW, Yoon YJ, Park ES. Comparison of butorphanol with morphine in intravenous patient controlled analgesia (pca) for postoperative pain relief. Korean Journal of Anesthesiology. 1997; 33(3):502-509

424. Hwang SH, Park IJ, Cho YJ, Jeong YM, Kang JM. The efficacy of gabapentin/pregabalin in improving pain after tonsillectomy: A meta-analysis. Laryngoscope. 2016; 126(2):357-66

425. Hynninen MS, Cheng DC, Hossain I, Carroll J, Aumbhagavan SS, Yue R et al. Non-steroidal anti-inflammatory drugs in treatment of postoperative pain after cardiac surgery. Canadian Journal of Anaesthesia. 2000; 47(12):1182-7

426. Idowu OA, Sanusi AA, Eyelade OR. Effects of intrathecally administered fentanyl on duration of analgesia in patients undergoing spinal anaesthesia for elective caesarean section. African Journal of Medicine and Medical Sciences. 2011; 40(3):213-9

427. Ilkjaer S, Nikolajsen L, Hansen TM, Wernberg M, Brennum J, Dahl JB. Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. British Journal of Anaesthesia. 1998; 81(5):707-12

428. Inan N, Cakan T, Ozen M, Aydin N, Gurel D, Baltaci B. The effect of opioid administration by different routes on the psychological functions of elderly patients. Agri. 2007; 19(4):32-8

429. Inthigood N, Lertbunnaphong T, Jaishuen A. Efficacy of a single 40-mg intravenous dose of parecoxib for postoperative pain control after elective cesarean delivery: A double-blind randomized placebo-controlled trial. Journal of Obstetrics and Gynaecology Research. 2017; 43(1):92-99

430. Ishiguro N, Hanaoka A, Okada T, Ito M. Efficacy and safety of celecoxib compared with placebo and etodolac for acute postoperative pain: a multicenter, double-blind, randomized, parallel-group, controlled trial. Nagoya Journal of Medical Science. 2015; 77(1-2):81-93

431. Isola G, Matarese M, Ramaglia L, Cicciu M, Matarese G. Evaluation of the efficacy of celecoxib and ibuprofen on postoperative pain, swelling, and mouth opening after surgical removal of impacted third molars: a randomized, controlled clinical trial. International Journal of Oral and Maxillofacial Surgery. 2019; Epublication

432. Issioui T, Klein KW, White PF, Watcha MF, Coloma M, Skrivanek GD et al. The efficacy of premedication with celecoxib and acetaminophen in preventing pain after otolaryngologic surgery. Anesthesia and Analgesia. 2002; 94(5):1188-93

433. Iwata M, Inoue S, Kawaguchi M, Kimura T, Tojo T, Taniguchi S et al. Ketamine eliminates propofol pain but does not affect hemodynamics during induction with double-lumen tubes. Journal of Anesthesia. 2010; 24(1):31-7

434. Jacobson L, Chabal C, Brody MC, Ward RJ, Ireton RC. Intrathecal methadone and morphine for postoperative analgesia: a comparison of the efficacy, duration, and side effects. Anesthesiology. 1989; 70(5):742-6

435. Jain AK, Ryan JR, McMahon FG, Smith G. Comparison of oral nalbuphine, acetaminophen, and their combination in postoperative pain. Clinical Pharmacology and Therapeutics. 1986; 39(3):295-9

436. Jain P, Jolly A, Bholla V, Adatia S, Sood J. Evaluation of efficacy of oral pregabalin in reducing postoperative pain in patients undergoing total knee arthroplasty. Indian Journal of Orthopaedics. 2012; 46(6):646-52

437. Jakobsson J, Rane K, Davidson S. Intramuscular NSAIDS reduce post-operative pain after minor outpatient anaesthesia. European Journal of Anaesthesiology. 1996; 13(1):67-71

438. Jaksch W, Lang S, Reichhalter R, Raab G, Dann K, Fitzal S. Perioperative small-dose S(+)-ketamine has no incremental beneficial effects on postoperative pain when standard-practice opioid infusions are used. Anesthesia and Analgesia. 2002; 94(4):981-6

439. Jarde O, Boccard E. Parenteral versus oral route increases paracetamol efficacy. Clinical Drug Investigation. 1997; 14(6):474-481

440. Jarraya A, Zghal J, Abidi S, Smaoui M, Kolsi K. Subarachnoid morphine versus TAP blocks for enhanced recovery after caesarean section delivery: A randomized controlled trial. Anaesthesia Critical Care & Pain Medicine. 2016; 35(6):391-393

441. Javery KB, Ussery TW, Steger HG, Colclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. Canadian Journal of Anaesthesia. 1996; 43(3):212-5

442. Jayr C, Beaussier M, Gustafsson U, Leteurnier Y, Nathan N, Plaud B et al. Continuous epidural infusion of ropivacaine for postoperative analgesia after major abdominal surgery: comparative study with I.V. PCA morphine. British Journal of Anaesthesia. 1998; 81(6):887-92

443. Jayr C, Thomas H, Rey A, Farhat F, Lasser P, Bourgain JL. Postoperative pulmonary complications. Epidural analgesia using bupivacaine and opioids versus parenteral opioids. Anesthesiology. 1993; 78(4):666-76; discussion 22A

444. Jendoubi A, Naceur IB, Bouzouita A, Trifa M, Ghedira S, Chebil M et al. A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: A prospective, double-blind, randomized, placebo-controlled study. Saudi Journal of Anaesthesia. 2017; 11(2):177-184

445. Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: a systematic review. Acta Anaesthesiologica Scandinavica. 2011; 55(6):638-43

446. Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M et al. Long-term pain prevalence and health-related quality of life outcomes for patients enrolled in a ketamine versus morphine for prehospital traumatic pain randomised controlled trial. Emergency Medicine Journal. 2014; 31(10):840-3

447. Jensen LL, Handberg G, Helbo-Hansen HS, Skaarup I, Lohse T, Munk T et al. No morphine sparing effect of ketamine added to morphine for patient-controlled intravenous analgesia after uterine artery embolization. Acta Anaesthesiologica Scandinavica. 2008; 52(4):479-86

448. Jeon EJ, Park YS, Park SS, Lee SK, Kim DH. The effectiveness of gabapentin on post-tonsillectomy pain control. European Archives of Oto-Rhino-Laryngology. 2009; 266(10):1605-9

449. Jeon HR, Chae WS, Lee SJ, Lee JH, Cho SH, Kim SH et al. A comparison of sufentanil and fentanyl for patient-controlled epidural analgesia in arthroplasty. Korean Journal of Anesthesiology. 2011; 60(1):41-6

450. Jespersen TW, Christensen KS, Kjaersgaard-Andersen P, Sommer S, Juhl B. Postoperative analgesia with morphine versus morphine and paracetamol. A double-blind clinically controlled study with a placebo. Ugeskrift for Laeger. 1989; 151(25):1615-1618

451. Jespersen TW, Christensen KS, Kjaersgaard-Andersen P, Sommer S, Juhl B. Treatment of postoperative pain with morphine compared with morphine and paracetamol. A double-blind clinically controlled investigation with a placebo. Ugeskrift for Laeger. 1989; 151(25):1615-1618

452. Jiang HL, Huang S, Song J, Wang X, Cao ZS. Preoperative use of pregabalin for acute pain in spine surgery. Medicine. 2017; 96 (11):e6129

453. Jiang HL, Huang S, Song J, Wang X, Cao ZS. Preoperative use of pregabalin for acute pain in spine surgery: A meta-analysis of randomized controlled trials. Medicine. 2017; 96(11):e6129

454. Jiang Y, Li J, Lin H, Huang Q, Wang T, Zhang S et al. The efficacy of gabapentin in reducing pain intensity and morphine consumption after breast cancer surgery: A meta-analysis. Medicine. 2018; 97(38):e11581

455. Johnson GH, Van Wagoner JD, Brown J, Cooper SA. Bromfenac sodium, acetaminophen/oxycodone, ibuprofen, and placebo for relief of postoperative pain. Clinical Therapeutics. 1997; 19(3):507-19

456. Johnson RG, Miller M, Murphy M. Intraspinal narcotic analgesia. A comparison of two methods of postoperative pain relief. Spine. 1989; 14(4):363-366

457. Joint Formulary Committee. British National Formulary (online). Available from: http://www.medicinescomplete.com Last accessed: 04/04/19

458. Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology. 2005; 103(1):147-55

459. Jonkman K, Dahan A, van de Donk T, Aarts L, Niesters M, van Velzen M. Ketamine for pain [version 1; peer review: 2 approved]. F1000Research. 1000; 6(F1000 Faculty Rev):1711

460. Jørgensen H, Fomsgaard JS, Dirks J, Wetterslev J, Andreasson B, Dahl JB. Effect of epidural bupivacaine vs combined epidural bupivacaine and morphine on gastrointestinal function and pain after major gynaecological surgery. British Journal of Anaesthesia. 2001; 87(5):727-732

461. Jorgensen H, Fomsgaard JS, Dirks J, Wetterslev J, Dahl JB. Effect of continuous epidural 0.2% ropivacaine vs 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy. British Journal of Anaesthesia. 2000; 84(2):144-50

462. Joris JL, Jacob EA, Sessler DI, Deleuse JF, Kaba A, Lamy ML. Spinal mechanisms contribute to analgesia produced by epidural sufentanil combined with bupivacaine for postoperative analgesia. Anesthesia and Analgesia. 2003; 97(5):1446-51

463. Joseph C, Gaillat F, Duponq R, Lieven R, Baumstarck K, Thomas P et al. Is there any benefit to adding intravenous ketamine to patient-controlled epidural analgesia after thoracic surgery? A randomized double-blind study. European Journal of Cardio-Thoracic Surgery. 2012; 42(4):e58-65

464. Joshi A, Parara E, Macfarlane TV. A double-blind randomised controlled clinical trial of the effect of preoperative ibuprofen, diclofenac, paracetamol with codeine and placebo tablets for relief of postoperative pain after removal of impacted third molars. British Journal of Oral and Maxillofacial Surgery. 2004; 42(4):299-306

465. Joshi GP, McCarroll SM, O'Rourke K. Postoperative analgesia after lumbar laminectomy: epidural fentanyl infusion versus patient-controlled intravenous morphine. Anesthesia and Analgesia. 1995; 80(3):511-4

466. Joshi SS, Jagadeesh AM. Efficacy of perioperative pregabalin in acute and chronic post-operative pain after off-pump coronary artery bypass surgery: a randomized, double-blind placebo controlled trial. Annals of Cardiac Anaesthesia. 2013; 16(3):180-5

467. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Medicine. 2015; 16(2):383-403

468. Jung JY, Bang KH, Kim SH, Kim YI. Influence of ketamine on the analgesic effect of epidural bupivacaine and fentanyl after a transabdominal hysterectomy. Korean Journal of Pain. 2005; 18(2):138-141

469. Jung KW, Kang HW, Park CH, Choi BH, Bang JY, Lee SH et al. Comparison of the analgesic effect of patient-controlled oxycodone and fentanyl for pain management in patients undergoing colorectal surgery. Clinical and Experimental Pharmacology and Physiology. 2016; 43(8):745-752

470. Kafali H, Aldemir B, Kaygusuz K, Gursoy S, Kunt N. Small-dose ketamine decreases postoperative morphine requirements. European Journal of Anaesthesiology. 2004; 21(11):916-7

471. Kahlenberg CA, Patel RM, Knesek M, Tjong VK, Sonn K, Terry MA. Efficacy of celecoxib for early postoperative pain management in hip arthroscopy: A prospective randomized placebo-controlled study. Arthroscopy. 2017; 33(6):1180-1185

472. Kahn L, Baxter FJ, Dauphin A, Goldsmith C, Jackson PA, McChesney J et al. A comparison of thoracic and lumbar epidural techniques for post-thoracoabdominal esophagectomy analgesia. Canadian Journal of Anaesthesia. 1999; 46(5 Pt 1):415-22

473. Kaiko R, Van Wagoner J, Brown J, O'Callaghan V, Grandy R, Hopf K et al. Controlled-release oral morphine (MS contin tablets, MSC) in postoperative pain. European Journal of Pharmacology. 1990; 183(4):1437-1438

474. Kaiko RF, Wallenstein SL, Rogers AG, Canel A, Jacobs B, Houde RW. Meptazinol and morphine in postoperative pain. International Journal of Clinical Pharmacology and Therapeutics. 1985; 37(2):203

475. Kainzwaldner V, Rachinger-Adam B, Mioc-Curic T, Wohrle T, Hinske LC, Luchting B et al. Quality of postoperative pain therapy: evaluation of an established anesthesiology acute pain service. Der Anaesthesist. 2013; 62(6):453-459

476. Kakehata J, Shibuya M, Yokota S, Takigawa C, Tsujinaga H, Tsutahara S et al. Efficacy of patient-controlled epidural analgesia using a disposable PCA device. Japanese Journal of Anesthesiology. 2000; 49(8):851-856

477. Kakinohana M, Higa Y, Sasara T, Saikawa S, Miyata Y, Tomiyama H et al. Addition of ketamine to propofol-fentanyl anaesthesia can reduce post-operative pain and epidural analgesic consumption in upper abdominal surgery. Acute Pain. 2004; 5(3-4):75-79

478. Kaloul I, Guay J, Cote C, Fallaha M. The posterior lumbar plexus (psoas compartment) block and the three-in-one femoral nerve block provide similar postoperative analgesia after total knee replacement. Canadian Journal of Anaesthesia. 2004; 51(1):45-51

479. Kamal HM. Ketamine as an adjuvant to morphine for patient controlled analgesia in morbidly obese patients. Journal of Medical Sciences. 2008; 8(4):364-370

480. Kammoun W, Mestiri T, Miraoui W, Frikha N, Mebazaa MS, Kilani T et al. Patient controlled epidural analgesia: interest in thoracic surgery. Tunisie Medicale. 2008; 86(2):144-149

481. Kampe S, Diefenbach C, Kanis B, Auweiler M, Kiencke P, Cranfield K. Epidural combination of ropivacaine with sufentanil for postoperative analgesia after total knee replacement: a pilot study. European Journal of Anaesthesiology. 2002; 19(9):666-71

482. Kampe S, Randebrock G, Kiencke P, Hunseler U, Cranfield K, Konig DP et al. Comparison of continuous epidural infusion of ropivacaine and sufentanil with intravenous patient-controlled analgesia after total hip replacement. Anaesthesia. 2001; 56(12):1189-93

483. Kampe S, Wolter K, Warm M, Dagtekin O, Shaheen S, Landwehr S. Clinical equivalence of controlled-release oxycodone 20 mg and controlled-release tramadol 200 mg after surgery for breast cancer. Pharmacology. 2009; 84(5):276-81

484. Kang KS, Kim CW, Ahn KR, Kim CS, Yoo S, Chung JH. A comparison of cervical epidural analgesia and intravenous patient-controlled analgesia after mastectomy with immediate latissimus dorsi flap breast reconstruction. Korean Journal of Anesthesiology. 2009; 56(6):669-674

485. Kapfer B, Alfonsi P, Guignard B, Sessler DI, Chauvin M. Nefopam and ketamine comparably enhance postoperative analgesia. Anesthesia and Analgesia. 2005; 100(1):169-74

486. Karaman S, Gunusen I, Uyar M, Firat V. The effect of pre-operative lornoxicam and ketoprofen application on the morphine consumption of post-operative patient-controlled analgesia. Journal of International Medical Research. 2006; 34(2):168-75

487. Karaman S, Kocabaş S, Zincircioğlu C, Firat V. Has ketamine preemptive analgesic effect in patients undergoing abdominal hysterectomy? Agri. 2006; 18(3):36-44

488. Kararmaz A, Kaya S, Karaman H, Turhanoglu S, Ozyilmaz MA. Intraoperative intravenous ketamine in combination with epidural analgesia: postoperative analgesia after renal surgery. Anesthesia and Analgesia. 2003; 97(4):1092-6

489. Kararmaz A, Kaya S, Karaman H, Turhanoglu S, Ozyilmaz MA. The Effects of the Type of Neuroaxial Block on Postoperative Pain after Total HIP Replacement Surgery: spinal vs. Epidural Anaesthesia. Turkish Journal of Anaesthesiology and Reanimation. 2004; 32(1):40-46

490. Karbic VO, Skoda M, Antoncic D, Kristofic I, Komar D, Trobonjaca Z. Gabapentin-induced changes of plasma cortisol level and immune status in hysterectomized women. International Immunopharmacology. 2014; 23(2):530-6

491. Karcioglu M, Davarci I, Tuzcu K, Bozdogan YB, Turhanoglu S, Aydogan A et al. Addition of ketamine to propofol-alfentanil anesthesia may reduce postoperative pain in laparoscopic cholecystectomy. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques. 2013; 23(2):197-202

492. Karst M, Kegel T, Lukas A, Ludemann W, Hussein S, Piepenbrock S. Effect of celecoxib and dexamethasone on postoperative pain after lumbar disc surgery. Neurosurgery. 2003; 53(2):331-6; discussion 336-7

493. Kashefi P. The benefits of intraoperative small-dose ketamine on postoperative pain after cesarean section. Anesthesiology. 2006; 104(Suppl 1):27

494. Kati I, Demirel CB, Abbasov UH, Silay E. Comparison of preemptive analgesic effects of epidural tramadol and morphine. Turkish Journal of Anaesthesiology and Reanimation. 2001; 29(3):124-128

495. Kati I, Demirel CB, Cirak B, Huseyinoglu UA. Epidural analgesia after lumbar disc surgery with ropivacaine plus fentanyl or bupivacaine plus fentanyl. Pain Clinic. 2005; 17(2):183-187

496. Katz J, Schmid R, Snijdelaar DG, Coderre TJ, McCartney CJ, Wowk A. Pre-emptive analgesia using intravenous fentanyl plus low-dose ketamine for radical prostatectomy under general anesthesia does not produce short-term or long-term reductions in pain or analgesic use. Pain. 2004; 110(3):707-18

497. Kawana Y, Sato H, Shimada H, Fujita N, Ueda Y, Hayashi A et al. Epidural ketamine for postoperative pain relief after gynecologic operations: a double-blind study and comparison with epidural morphine. Anesthesia and Analgesia. 1987; 66(8):735-8

498. Kay B, Healy TE. Premedication by controlled-release morphine. Anaesthesia. 1984; 39(6):587-9

499. Kellstein D, Ott D, Jayawardene S, Fricke J. Analgesic efficacy of a single dose of lumiracoxib compared with rofecoxib, celecoxib and placebo in the treatment of post-operative dental pain. International Journal of Clinical Practice. 2004; 58(3):244-50

500. Kentner R, Heinrichs W, Dick W. Combination of intravenous patient-controlled analgesia with epidural anesthesia for postoperative pain therapy. Anaesthesiologie und Reanimation. 1996; 21(3):69-75

501. Kerrick JM, Fine PG, Lipman AG, Love G. Low-dose amitriptyline as an adjunct to opioids for postoperative orthopedic pain: a placebo-controlled trial. Pain. 1993; 52(3):325-30

502. Khademi S, Ghaffarpasand F, Heiran HR, Asefi A. Effects of preoperative gabapentin on postoperative nausea and vomiting after open cholecystectomy: a prospective randomized double-blind placebo-controlled study. Medical Principles and Practice. 2010; 19(1):57-60

503. Khalili GR, Karimi MA. Comparison of intravenous and epidural patient-controlled analgesia after knee and hip arthroplasty. Journal of Isfahan Medical School. 2012; 30(178)

504. Khan AA, Brahim JS, Rowan JS, Dionne RA. In vivo selectivity of a selective cyclooxygenase 2 inhibitor in the oral surgery model. Clinical Pharmacology and Therapeutics. 2002; 72(1):44-9

505. Khan MA, Siddiqi KJ, Aqeel M. Effect of gabapentin on opioid requirements in patients undergoing total abdominal hysterectomy. Anaesthesia, Pain and Intensive Care. 2013; 17(2):131-135

506. Khan ZH, Rahimi M, Makarem J, Khan RH. Optimal dose of pre-incision/post-incision gabapentin for pain relief following lumbar laminectomy: a randomized study. Acta Anaesthesiologica Scandinavica. 2011; 55(3):306-12

507. Khashan M, Dolkart O, Amar E, Chechik O, Sharfman Z, Mozes G et al. Effect of preemptive intra-articular morphine and ketamine on pain after arthroscopic rotator cuff repair: a prospective, double-blind, randomized controlled study. Archives of Orthopaedic and Trauma Surgery. 2016; 136(2):233-9

508. Khurana G, Jindal P, Sharma JP, Bansal KK. Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. Spine. 2014; 39(6):E363-8

509. Kiersch TA, Halladay SC, Koschik M. A double-blind, randomized study of naproxen sodium, ibuprofen, and placebo in postoperative dental pain. Clinical Therapeutics. 1993; 15(5):845-54

510. Kikuchi S, Kuroda S, Nishizaki M, Matsusaki T, Mitsuhashi T, Kuwada K et al. Randomized controlled trial of epidural versus patient-controlled intravenous analgesia for postoperative pain control after laparoscopic gastrectomy. Acta Medica Okayama. 2018; 72(1):95-98

511. Kim CJ, Chea JS, Chung MY, Song DH, Park JJ, Lee BH. The analgesic effect of combined infusions of morphine and ketamine using an intravenous pca after a cesarean section. Korean Journal of Anesthesiology. 2001; 40(4):509-514

512. Kim DH, Kwak SH, Yang SH, Jeong SW, Yoon MH, Jeong CY. A comparison of epidural fentanyl-bupivacaine and intravenous morphine using patient-controlled analgesia after thoracic surgery. Korean Journal of Anesthesiology. 1999; 36(5):846-855

513. Kim DY, An YM, Moon JP, Choi JG. Effect of preoperative administration of celecoxib on postoperative pain after laparoscopic cholecystectomy. Korean Journal of Anesthesiology. 2009; 57(3):327-330

514. Kim HC, Bae JY, Kim TK, Jeon Y, Min JJ, Goo EK et al. Efficacy of intrathecal morphine for postoperative pain management following open nephrectomy. Journal of International Medical Research. 2016; 44(1):42-53

515. Kim HM, Kim EO, Song JE, Park SH, Jun HA, Kim H. Effectiveness of preemptive Gabapentin on postoperative pain after vaginal hysterectomy. Korean Journal of Obstetrics and Gynecology. 2008; 51(3):305-312

516. Kim HY, Yoon HS. The effects of ketamine preemptive analgesia on postoperative pain in patients undergoing a hysterectomy. Taehan Kanho Korean Nurse. 2006; 36(1):114-126

517. Kim JA, Kim TH, Yang M, Gwak MS, Kim GS, Kim MJ et al. Is intravenous patient controlled analgesia enough for pain control in patients who underwent thoracoscopy? Journal of Korean Medical Science. 2009; 24(5):930-935

518. Kim JC, Byun S, Kim S, Lee SY, Lee JH, Ahn S. Effect of preoperative pregabalin as an adjunct to a multimodal analgesic regimen in video-assisted thoracoscopic surgery: A randomized controlled trial. Medicine. 2017; 96(49):e8644

519. Kim JC, Choi YS, Kim KN, Shim JK, Lee JY, Kwak YL. Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. Spine. 2011; 36(6):428-33

520. Kim JH, Seo MY, Hong SD, Lee J, Chung SK, Kim HY et al. The efficacy of preemptive analgesia with pregabalin in septoplasty. Clinical and Experimental Otorhinolaryngology. 2014; 7(2):102-5

521. Kim JY, Lee SJ, Koo BN, Noh SH, Kil HK, Kim HS et al. The effect of epidural sufentanil in ropivacaine on urinary retention in patients undergoing gastrectomy. British Journal of Anaesthesia. 2006; 97(3):414-8

522. Kim NS, Kang KS, Yoo SH, Chung JH, Chung JW, Seo Y et al. A comparison of oxycodone and fentanyl in intravenous patient-controlled analgesia after laparoscopic hysterectomy. Korean Journal of Anesthesiology. 2015; 68(3):261-6

523. Kim NS, Lee JS, Park SY, Ryu A, Chun HR, Chung HS et al. Oxycodone versus fentanyl for intravenous patient-controlled analgesia after laparoscopic supracervical hysterectomy: A prospective, randomized, double-blind study. Medicine. 2017; 96(10):e6286

524. Kim NY, Kim SY, Ju HM, Kil HK. Selective spinal anesthesia using 1 mg of bupivacaine with opioid in elderly patients for transurethral resection of prostate. Yonsei Medical Journal. 2015; 56(2):535-42

525. Kim SH, Kim SI, Ok SY, Park SY, Kim MG, Lee SJ et al. Opioid sparing effect of low dose ketamine in patients with intravenous patient-controlled analgesia using fentanyl after lumbar spinal fusion surgery. Korean Journal of Anesthesiology. 2013; 64(6):524-8

526. Kim SI, Park DY, Ok SY, Kim SC. Effects of preemptive gabapentin on postoperative pain after mastectomy. Korean Journal of Anesthesiology. 2004; 47(4):527-531

527. Kim SY, Jeong JJ, Chung WY, Kim HJ, Nam KH, Shim YH. Perioperative administration of pregabalin for pain after robot-assisted endoscopic thyroidectomy: a randomized clinical trial. Surgical Endoscopy. 2010; 24(11):2776-81

528. Kim SY, Song JW, Park B, Park S, An YJ, Shim YH. Pregabalin reduces post-operative pain after mastectomy: a double-blind, randomized, placebo-controlled study. Acta Anaesthesiologica Scandinavica. 2011; 55(3):290-6

529. Kinney MA, Mantilla CB, Carns PE, Passe MA, Brown MJ, Hooten WM et al. Preoperative gabapentin for acute post-thoracotomy analgesia: a randomized, double-blinded, active placebo-controlled study. Pain Practice. 2012; 12(3):175-83

530. Kiya T, Fujimura N, Okanuma M, Namiki A. Effect of continuous extradural infusion of bupivacaine on diaphragmatic function after upper abdominal surgery. Japanese Journal of Anesthesiology. 2003; 52(5):500-504

531. Kjaer Petersen K, Lunn TH, Husted H, Hansen LT, Simonsen O, Laursen MB et al. The influence of pre- and perioperative administration of gabapentin on pain 3-4 years after total knee arthroplasty. Scandinavian Journal of Pain. 2018; 18(2):237-245

532. Kjolhede P, Bergdahl O, Borendal Wodlin N, Nilsson L. Effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy: an open-label randomised trial. BMJ Open. 2019; 9(3):e024484

533. Klasen JA, Opitz SA, Melzer C, Thiel A, Hempelmann G. Intraarticular, epidural, and intravenous analgesia after total knee arthroplasty. Acta Anaesthesiologica Scandinavica. 1999; 43(10):1021-6

534. Klatt E, Zumbrunn T, Bandschapp O, Girard T, Ruppen W. Intra- and postoperative intravenous ketamine does not prevent chronic pain: A systematic review and meta-analysis. Scandinavian Journal of Pain. 2015; 7(1):42-54

535. Klatt JWB, Mickelson J, Hung M, Durcan S, Miller C, Smith JT. A randomized prospective evaluation of 3 techniques of postoperative pain management after posterior spinal instrumentation and fusion. Spine. 2013; 38(19):1626-1631

536. Kluba T, Hofmann F, Bredanger S, Blumenstock G, Niemeyer T. Efficacy of post-operative analgesia after posterior lumbar instrumented fusion for degenerative disc disease: a prospective randomized comparison of epidural catheter and intravenous administration of analgesics. Orthopedic Reviews. 2010; 2(1):e9

537. Kochhar A, Banday J, Ahmad Z, Monga S, Vajifdar H. Pregabalin in Monitored Anesthesia Care for Ear-nose-throat Surgery. Anesthesia Essays and Researches. 2017; 11(2):350-353

538. Kochhar A, Chouhan K, Panjiar P, Vajifdar H. Gabapentinoids as a Part of Multi-modal Drug Regime for Pain Relief following Laproscopic Cholecystectomy: A Randomized Study. Anesthesia Essays and Researches. 2017; 11(3):676-680

539. Kogan A, Medalion B, Raanani E, Sharoni E, Stamler A, Pak N et al. Early oral analgesia after fast-track cardiac anesthesia. Canadian Journal of Anaesthesia. 2007; 54(4):254-61

540. Kohli M, Murali T, Gupta R, Khan P, Bogra J. Optimization of subarachanoid block by oral pregabalin for hysterectomy. Journal of Anaesthesiology Clinical Pharmacology. 2011; 27(1):101-5

541. Kollender Y, Bickels J, Stocki D, Maruoani N, Chazan S, Nirkin A et al. Subanaesthetic ketamine spares postoperative morphine and controls pain better than standard morphine does alone in orthopaedic-oncological patients. European Journal of Cancer. 2008; 44(7):954-62

542. Konishi A, Kikuchi K. Postoperative management following open heart surgery by thoracic epidural anesthesia. Japanese Journal of Anesthesiology. 1995; 44(8):1113-1117

543. Konstantatos AH, Howard W, Story D, Mok LY, Boyd D, Chan MT. A randomised controlled trial of peri-operative pregabalin vs. placebo for video-assisted thoracoscopic surgery. Anaesthesia. 2016; 71(2):192-7

544. Konstantatos AH, Kavnoudias H, Stegeman JR, Boyd D, Street M, Bailey M et al. A randomized, double-blind, placebo-controlled study of preemptive oral oxycodone with morphine patient-controlled anesthesia for postoperative pain management in patients undergoing uterine artery embolization for symptomatic uterine fibroids. Cardiovascular and Interventional Radiology. 2014; 37(5):1191-7

545. Kontrimaviciute E, Sipylaite J, Aksionova D, Cincileviciute G, Brimas G. Comparison of different anesthetic regimens in patients undergoing laparoscopic adjustable gastric banding operations: a prospective randomized trial. Medicina. 2012; 48(12):613-8

546. Kose EA, Honca M, Dal D, Akinci SB, Aypar U. Prophylactic ketamine to prevent shivering in parturients undergoing cesarean delivery during spinal anesthesia. Journal of Clinical Anesthesia. 2013; 25(4):275-280

547. Kossmann B, Dick W, Wollinsky KH, Traub E, Harzenetter J, Möller MR. Peridural morphine analgesia: effects and pharmacokinetics. A double-blind study in vaginal hysterectomy patients. Der Anaesthesist. 1983; 32(6):284-288

548. Kostamovaara PA, Hendolin H, Kokki H, Nuutinen LS. Ketorolac, diclofenac and ketoprofen are equally efficacious for pain relief after total hip replacement surgery. British Journal of Anaesthesia. 1998; 81(3):369-72

549. Kostamovaara PA, Laurila JJ, Alahuhta S, Salomaki TE. Ropivacaine 1 mg x ml(-1) does not decrease the need for epidural fentanyl after hip replacement surgery. Acta Anaesthesiologica Scandinavica. 2001; 45(4):489-94

550. Koşucu M. The effects of the pre-emptive oral gabapentin on post-anesthesia recovery criteria, acute post-thoracotomy pain and development of chronicity in pain with benign thoracotomy operations. Turkish Journal of Thoracic and Cardiovascular Surgery. 2014; 22(2):389-396

551. Kotsovolis G, Karakoulas K, Grosomanidis V, Tziris N. Comparison between the combination of gabapentin, ketamine, lornoxicam, and local ropivacaine and each of these drugs alone for pain after laparoscopic cholecystectomy: a randomized trial. Pain Practice. 2015; 15(4):355-63

552. Kowalski S, Ong B, Bell D, OStryzniuk T, Serrette C, Wasylak T. Postoperative analgesia and pulmonary function following upper abdominal surgery: epidural fentanyl versus PCA morphine. Canadian Journal of Anaesthesia. 1992; 39(5 (Suppl 2)):A58

553. Koyuncu T, Oğuz G, Akben S, Nas S, Ünver S. The effects of pregabaline on postoperative pain and opioid consumption used perioperatively in patients undergoing modified radical mastectomy. Agri. 2013; 25(4):169-178

554. Kroon UB, Radstrom M, Hjelthe C, Dahlin C, Kroon L. Fast-track hysterectomy: a randomised, controlled study. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2010; 151(2):203-7

555. Kuang MJ, Ma JX, Wang Y, Zhao J, Lu B, Ma XL. Efficacy of perioperative celecoxib use in primary total knee and hip arthroplasty: A meta-analysis. International Journal of Clinical and Experimental Medicine. 2016; 9(5):7719-7728

556. Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. Anesthesia and Analgesia. 2002; 95(1):114-8

557. Kuhnle MD, Ryan DS, Coe CD, Eaddy J, Kuzmowych C, Edwards J et al. Oral gabapentin for photorefractive keratectomy pain. Journal of Cataract and Refractive Surgery. 2011; 37(2):364-9

558. Kumar B, Ramakrishnappa SK, Bekal M. A randomized clinical study comparing the analgesic efficacy of intra venous patient- controlled analgesia of morphine with fentanyl in post-operative pain management of major surgery patients. National Journal of Physiology, Pharmacy and Pharmacology. 2017; 7(12):1422-1427

559. Kumar KP, Kulkarni DK, Gurajala I, Gopinath R. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: a randomized, double-blinded, placebo-controlled study. Journal of Pain Research. 2013; 6:471-8

560. Kumari I, Pathania VS. A prospective randomised double-blind placebo controlled trial of oral gabapentin in attenuation of haemodynamic responses during laryngoscopy and tracheal intubation. Journal of Anaesthesiology Clinical Pharmacology. 2009; 25(4):439-443

561. Kupers R, Callebaut V, Debois V, Camu F, Verborgh C, Coppejans H et al. Efficacy and safety of oral tramadol and pentazocine for postoperative pain following prolapsed intervertebral disc repair. Acta Anaesthesiologica Belgica. 1995; 46(1):31-7

562. Kwok RF, Lim J, Chan MT, Gin T, Chiu WK. Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. Anesthesia and Analgesia. 2004; 98(4):1044-9

563. Kwon OS, Lee HJ, Yoon JY, Kim CH, Kwon JY, Kim H. Intraoperative low dose ketamine reduce postoperative pain after combined anesthesia with propofol and remifentanil in mastectomy patients. Korean Journal of Anesthesiology. 2009; 57(5):604-609

564. Kwon YS, Jang JS, Lee NR, Kim SS, Kim YK, Hwang BM et al. A comparison of oxycodone and alfentanil in intravenous patient-controlled analgesia with a time-scheduled decremental infusion after laparoscopic cholecystectomy. Pain Research & Management. 2016; 2016:7868152

565. Lahtinen P, Kokki H, Hakala T, Hynynen M. S(+)-ketamine as an analgesic adjunct reduces opioid consumption after cardiac surgery. Anesthesia and Analgesia. 2004; 99(5):1295-301

566. Lak M, Foroozanmehr MJ, Ramazani MA, Araghizadeh H, Zahedi-Shoolami L. Assessment of ketamine effect as adjuvant to morphine in post-operative pain reduction in donor kidney transplanted. Iranian Red Crescent Medical Journal. 2010; 12(1):38-44

567. Lalenoh LAP. The antinociceptive effects of pregabalin on post-operative hysterectomy patient. Journal of Anesthesia & Clinical Research. 2014; 5:466

568. Lam DM, Choi SW, Wong SS, Irwin MG, Cheung CW. Efficacy of pregabalin in acute postoperative pain under different surgical categories: A meta-analysis. Medicine. 2015; 94(46):e1944

569. Lam FY, Broome IJ, Matthews PJ. A comparison of postoperative analgesia following spinal or epidural anaesthesia for caesarean section. Anaesthesia. 1994; 49(1):65-7

570. Lane S, Evans P, Arfeen Z, Misra U. A comparison of intrathecal fentanyl and diamorphine as adjuncts in spinal anaesthesia for caesarean section. Anaesthesia. 2005; 60(5):453-7

571. Lange M, Lee CW, Knisely T, Perla S, Barber K, Kia M. Efficacy of intravenous acetaminophen in length of stay and postoperative pain control in laparoscopic Roux-en-Y gastric bypass surgery patients. Bariatric Surgical Practice & Patient Care. 2018; 13(3):103-108

572. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Canadian Journal of Anaesthesia. 2011; 58(10):911-23

573. Lattermann R, Wykes L, Eberhart L, Carli F, Meterissian S, Schricker T. A randomized controlled trial of the anticatabolic effect of epidural analgesia and hypocaloric glucose. Regional Anesthesia and Pain Medicine. 2007; 32(3):227-32

574. Launo C, Bassi C, Spagnolo L, Badano S, Ricci C, Lizzi A et al. Preemptive ketamine during general anesthesia for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. Minerva Anestesiologica. 2004; 70(10):727-34; 734-8

575. Lauretti GR, Azevedo VM. Intravenous ketamine or fentanyl prolongs postoperative analgesia after intrathecal neostigmine. Anesthesia and Analgesia. 1996; 83(4):766-70

576. Laveneziana D, Riva A, Bonazzi M, Cipolla M, Migliavacca S. Comparative efficacy of oral ibuprofen arginine and intramuscular ketorolac in patients with postoperative pain. Clinical Drug Investigation. 1996; 11(Suppl. 1):8-14

577. Leal PC, Sakata RK, Salomao R, Sadatsune EJ, Issy AM. Assessment of the effect of ketamine in combination with remifentanil on postoperative pain. Brazilian Journal of Anesthesiology. 2013; 63(2):178-82

578. Leal PC, Salomao R, Brunialti MK, Sakata RK. Evaluation of the effect of ketamine on remifentanil-induced hyperalgesia: a double-blind, randomized study. Journal of Clinical Anesthesia. 2015; 27(4):331-337

579. Lebovits AH, Zenetos P, O'Neill DK, Cox D, Dubois MY, Jansen LA et al. Satisfaction with epidural and intravenous patient-controlled analgesia. Pain Medicine. 2001; 2(4):280-6

580. Lebrun T, Van Elstraete AC, Sandefo I, Polin B, Pierre-Louis L. Lack of a pre-emptive effect of low-dose ketamine on postoperative pain following oral surgery. Canadian Journal of Anaesthesia. 2006; 53(2):146-52

581. Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD002765. DOI: https://doi.org/10.1002/14651858.CD002765.pub3.

582. Lee A, McKeown D, Brockway M, Bannister J, Wildsmith JA. Comparison of extradural and intravenous diamorphine as a supplement to extradural bupivacaine. Anaesthesia. 1991; 46(6):447-50

583. Lee A, Simpson D, Whitfield A, Scott DB. Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. British Journal of Anaesthesia. 1988; 60(7):845-50

584. Lee BH, Chea JS, Chung MY, Byun HJ. A comparative effect of meperidine between intravenous and epidural patient-controlled analgesia for the postoperative pain relief after cesarean section. Journal of the Korean Pain Society. 1995; 8(2):257-265

585. Lee C, Lee HW, Kim JN. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. Korean Journal of Anesthesiology. 2013; 64(1):19-24

586. Lee EM, Lee H, Kim CH, Lee GY. A double-blinded, randomized, placebo controlled study of the effect a small dose of ketamine has on postoperative pain of sevoflurane-remifentanil anesthesia. Korean Journal of Anesthesiology. 2008; 54(2):146-151

587. Lee HD, Kim HK, Lee SN, Lee SY, Lee JH, Park DH. The effect of low dose i.V. Ketamine in combination with epidural morphine on postoperative pain. Korean Journal of Anesthesiology. 2005; 49(1):81-85

588. Lee HJ, Sung CH. Effect of epidural ketamine combined with bupivacaine and meperidine on postoperative pain and analgesic consumption after cesarean section. Korean Journal of Anesthesiology. 2001; 41(1):39-46

589. Lee JH, Lee HK, Chun NH, So Y, Lim CY. The prophylactic effects of gabapentin on postoperative sore throat after thyroid surgery. Korean Journal of Anesthesiology. 2013; 64(2):138-42

590. Lee JH, Park JH, Kil HK, Choi SH, Noh SH, Koo BN. Efficacy of intrathecal morphine combined with intravenous analgesia versus thoracic epidural analgesia after gastrectomy. Yonsei Medical Journal. 2014; 55(4):1106-14

591. Lee LH, Irwin MG, Lim J, Wong CK. The effect of celecoxib on intrathecal morphine-induced pruritus in patients undergoing Caesarean section. Anaesthesia. 2004; 59(9):876-80

592. Lee MH, Chung MH, Han CS, Lee JH, Choi YR, Choi EM et al. Comparison of effects of intraoperative esmolol and ketamine infusion on acute postoperative pain after remifentanil-based anesthesia in patients undergoing laparoscopic cholecystectomy. Korean Journal of Anesthesiology. 2014; 66(3):222-9

593. Lee SM, Lee JU, Shin HB, Lee WH. A comparison of the analgesic and side effects of continuous epidural morphine and nalbuphine after a cesarean section. Korean Journal of Anesthesiology. 2001; 41(1):59-65

594. Lee YS, Baek CW, Kim DR, Kang H, Choi GJ, Park YH et al. Comparison of hemodynamic response to tracheal intubation and postoperative pain in patients undergoing closed reduction of nasal bone fracture under general anesthesia: a randomized controlled trial comparing fentanyl and oxycodone. BMC Anesthesiology. 2016; 16:115

595. Lehmann KA, Klaschik M. Lack of pre-emptive analgesic effect of low-dose ketamine in postoperative patients. A prospective, randomised double-blind study. Schmerz. 2001; 15(4):248-253

596. Lena P, Balarac N, Arnulf JJ, Teboul J, Bonnet F. Intrathecal morphine and clonidine for coronary artery bypass grafting. British Journal of Anaesthesia. 2003; 90(3):300-3

597. Lenz H, Raeder J. Comparison of etoricoxib vs. ketorolac in postoperative pain relief. Acta Anaesthesiologica Scandinavica. 2008; 52(9):1278-84

598. Lenz H, Sandvik L, Qvigstad E, Bjerkelund CE, Raeder J. A comparison of intravenous oxycodone and intravenous morphine in patient-controlled postoperative analgesia after laparoscopic hysterectomy. Anesthesia and Analgesia. 2009; 109(4):1279-83

599. Lenzmeier B, Moore RL, Cordts P, Garrett N. Menstrual cycle-related variations in postoperative analgesia with the preemptive use of N-methyl D-aspartate antagonist ketamine: a pilot study. Dimensions of Critical Care Nursing. 2008; 27(6):271-6

600. Leung JM, Sands LP, Chen N, Ames C, Berven S, Bozic K et al. Perioperative gabapentin does not reduce postoperative delirium in older surgical patients: A randomized clinical trial. Anesthesiology. 2017; 127(4):633-644

601. Leung JM, Sands LP, Rico M, Petersen KL, Rowbotham MC, Dahl JB et al. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology. 2006; 67(7):1251-3

602. Levanen J. Ketamine and oxycodone in the management of postoperative pain. Military Medicine. 2000; 165(6):450-5

603. Levin HM, Bare WW, Berry FN, Miller JM. Acetaminophen with codeine for the relief of severe pain in postpartum patients. Current Therapeutic Research, Clinical and Experimental. 1974; 16(9):921-7

604. Levy BF, Tilney HS, Dowson HM, Rockall TA. A systematic review of postoperative analgesia following laparoscopic colorectal surgery. Colorectal Disease. 2010; 12(1):5-15

605. Lew E, Yeo SW, Thomas E. Combined spinal-epidural anesthesia using epidural volume extension leads to faster motor recovery after elective cesarean delivery: a prospective, randomized, double-blind study. Anesthesia and Analgesia. 2004; 98(3):810-4

606. Leykin Y, Casati A, Rapotec A, Dal Sasso M, Barzan L, Fanelli G et al. A prospective, randomized, double-blind comparison between parecoxib and ketorolac for early postoperative analgesia following nasal surgery. Minerva Anestesiologica. 2008; 74(9):475-9

607. Li ALK, Wadsworth K, Siddiqui NT, Alarab M, McDermott CD, Lemos N et al. Does low-dose gapapentin reduce opioid use postoperatively?: A randomized controlled trial in women undergoing reconstructive pelvic surgery. International Urogynecology Journal. 2018; 30(2):211-217

608. Li M, Li L, Xu YT, Wang X. Intravenous analgesics for pain management in postoperative patients: A comparative study of their efficacy and adverse effects. Tropical Journal of Pharmaceutical Research. 2016; 15(8):1799-1806

609. Li S, Guo J, Li F, Yang Z, Wang S, Qin C. Pregabalin can decrease acute pain and morphine consumption in laparoscopic cholecystectomy patients: A meta-analysis of randomized controlled trials. Medicine. 2017; 96(21):e6982

610. Li XD, Han C, Yu WL. Is gabapentin effective and safe in open hysterectomy? A PRISMA compliant meta-analysis of randomized controlled trials. Journal of Clinical Anesthesia. 2017; 41:76-83

611. Li Y, Lu S, Ma SC, Fan HW, Zhao GQ. Effects of patient-controlled epidural analgesia and patient-controlled intravenous analgesia on analgesia in patients undergoing spinal fusion surgery. American Journal of Therapeutics. 2016; 23(6):e1806-e1812

612. Liashek P, Jr., Desjardins PJ, Triplett RG. Effect of pretreatment with acetaminophen-propoxyphene for oral surgery pain. Journal of Oral and Maxillofacial Surgery. 1987; 45(2):99-103

613. Lichtinger A, Purcell TL, Schanzlin DJ, Chayet AS. Gabapentin for postoperative pain after photorefractive keratectomy: a prospective, randomized, double-blind, placebo-controlled trial. Journal of Refractive Surgery. 2011; 27(8):613-617

614. Lierz P, Losch H, Felleiter P. Evaluation of a single preoperative dose of etoricoxib for postoperative pain relief in therapeutic knee arthroscopy: a randomized trial. Acta Orthopaedica. 2012; 83(6):642-7

615. Lim Y, Wilson S, Katz S. A comparison of patient-controlled epidural pethidine vs. nurse-administered epidural pethidine for analgesia after caesarean section. Journal of Opioid Management. 2006; 2(2):99-104

616. Limberi S, Markou N, Sakayianni K, Vourliotou A, Kremastinou F, Savari E et al. Coronary artery disease and upper abdominal surgery: impact of anesthesia on perioperative myocardial ischemia. Hepato-Gastroenterology. 2003; 50(54):1814-20

617. Lin FS, Lin WY, Lai CH, Chen CY, Lin CP, Lin TF et al. Analgesic efficacy of tramadol/acetaminophen and propoxyphene/acetaminophen for relief of postoperative wound pain. Acta Anaesthesiologica Taiwanica 2012; 50(2):49-53

618. Lin HQ, Jia DL. Effect of preemptive ketamine administration on postoperative visceral pain after gynecological laparoscopic surgery. Journal of Huazhong University of Science and Technology Medical Sciences. 2016; 36(4):584-587

619. Lionberger DR, Noble PC. Celecoxib does not affect osteointegration of cementless total hip stems. Journal of Arthroplasty. 2005; 20(Suppl. 3):115-122

620. Lippmann M, Mok M, Steen S. A placebo-controlled study of butorphanol and acetaminophen in postoperative pain. International Journal of Clinical Pharmacology and Therapeutics. 1980; 27(2):267

621. Liu B, Liu R, Wang L. A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery. Medicine. 2017; 96(37):e8031

622. Liu N, Kuhlman G, Dalibon N, Moutafis M, Levron JC, Fischler M. A randomized, double-blinded comparison of intrathecal morphine, sufentanil and their combination versus IV morphine patient-controlled analgesia for postthoracotomy pain. Anesthesia and Analgesia. 2001; 92(1):31-6

623. Liu P, Wu Y, Liang Z, Deng Y, Meng Q. Comparing the efficacy of pain managements after total hip arthroplasty: A network meta-analysis. Journal of Cellular Biochemistry. 2019; 120(3):4342-4354

624. Liu Q, Zhao JN, Chen HX, Zhong TD. Oral controlled-release oxycodone for uterine cramping pain after cesarean section. Chinese Medical Journal (Taipei). 2011; 91(30):2132-2134

625. Liu S, Carpenter RL, Mulroy MF, Weissman RM, McGill TJ, Rupp SM et al. Intravenous versus epidural administration of hydromorphone. Effects on analgesia and recovery after radical retropubic prostatectomy. Anesthesiology. 1995; 82(3):682-8

626. Liu SS, Carpenter RL, Mackey DC, Thirlby RC, Rupp SM, Shine TS et al. Effects of perioperative analgesic technique on rate of recovery after colon surgery. Anesthesiology. 1995; 83(4):757-65

627. Liu W, Loo CC, Chiu JW, Tan HM, Ren HZ, Lim Y. Analgesic efficacy of pre-operative etoricoxib for termination of pregnancy in an ambulatory centre. Singapore Medical Journal. 2005; 46(8):397-400

628. Liu W, Xing Y, Li J. Effect of two tramadol administration methods on postoperative breast cancer pain. Chinese Journal of Clinical Oncology. 2012; 39(14):990-992

629. Liu WF, Shu HH, Zhao GD, Peng SL, Xiao JF, Zhang GR et al. Effect of parecoxib as an adjunct to patient-controlled epidural analgesia after abdominal hysterectomy: A multicenter, randomized, placebo-controlled trial. PloS One. 2016; 11(9):e0162589

630. Liu Y, Zheng Y, Gu X, Ma Z. The efficacy of NMDA receptor antagonists for preventing remifentanil-induced increase in postoperative pain and analgesic requirement: a meta-analysis. Minerva Anestesiologica. 2012; 78(6):653-67

631. Liu YH, Fan ZY, Jin YY, Hu YH. Efficacy and safty of oxycodone hydrochloride injection for general anesthetic recovery. Chinese Journal of New Drugs. 2015; 24(4):427-429 and 446

632. Lo A, Macpherson N, Spiwak R. Prospective randomized trial of patient-controlled analgesia with ketamine and morphine or morphine alone after hysterectomy. Canadian Journal of Hospital Pharmacy. 2008; 61(5):334-339

633. Loane H, Preston R, Douglas MJ, Massey S, Papsdorf M, Tyler J. A randomized controlled trial comparing intrathecal morphine with transversus abdominis plane block for post-cesarean delivery analgesia. International Journal of Obstetric Anesthesia. 2012; 21(2):112-8

634. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010; 113(3):639-46

635. Logas WG, el-Baz N, el-Ganzouri A, Cullen M, Staren E, Faber LP et al. Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy: a randomized prospective study. Anesthesiology. 1987; 67(5):787-91

636. Lohit K, Srinivas V, Kulkarni C, Shaheen. A clinical evaluation of the effects of administration of midazolam on ketamine- induced emergence phenomenon. Journal of Clinical and Diagnostic Research. 2011; 5(2):320-323

637. Loper KA, Ready LB, Downey M, Sandler AN, Nessly M, Rapp S et al. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesthesia and Analgesia. 1990; 70(1):72-5

638. Lorenzini C, Moreira LB, Ferreira MB. Efficacy of ropivacaine compared with ropivacaine plus sufentanil for postoperative analgesia after major knee surgery. Anaesthesia. 2002; 57(5):424-8

639. Lou QB, Nan K, Xiang FF, Chen XZ, Zhu WS, Zhang XT et al. Effect of perioperative multi-day low dose ketamine infusion on prevention of postmastectomy pain syndrome. Chinese Medical Journal (Taipei). 2017; 97(46):3636-3641

640. Lubenow TR, Tanck EN, Hopkins EM, McCarthy RJ, Ivankovich AD. Comparison of patient-assisted epidural analgesia with continuous-infusion epidural analgesia for postoperative patients. Regional Anesthesia. 1994; 19(3):206-11

641. Lund I, Hoel E, Vaagenes P. Analgesic potency of pentazocine and pethidine in post-operative pain. Journal of the Oslo City Hospitals. 1971; 21(9):132-9

642. Lunn TH, Husted H, Laursen MB, Hansen LT, Kehlet H. Analgesic and sedative effects of perioperative gabapentin in total knee arthroplasty: a randomized, double-blind, placebo-controlled dose-finding study. Pain. 2015; 156(12):2438-48

643. Luo H-G, Mei H-T, Che J-H, Zhang M-S, Xiao C-L. Antiemetic effect of gabapentin in patients undergoing laparoscopic cholecystectomy. China Journal of Endoscopy. 2009; 15(5):492-494

644. Luscombe KS, McDonnell NJ, Muchatuta NA, Paech MJ, Nathan EA. A randomised comparison of parecoxib versus placebo for pain management following minor day stay gynaecological surgery. Anaesthesia and Intensive Care. 2010; 38(1):141-8

645. Lutti MN, Simoni RF, Cangiani LM, Vieira JL, Silva LA. Patient controlled analgesia with morphine or fentanyl in knee ligament reconstruction postoperative period. A comparative study. Revista Brasileira de Anestesiologia. 2000; 50(1):8-13

646. Ma C, Zhou P. Comparison between patient-controlled epidural analgesia (PCEA) with patient-controlled intravenous analgesia (PCIA) after operation on lung cancer. Chinese Journal of Clinical Oncology. 2005; 32(15):883-884+888

647. Macario A, Lipman AG. Ketorolac in the era of cyclo-oxygenase-2 selective nonsteroidal anti-inflammatory drugs: a systematic review of efficacy, side effects, and regulatory issues. Pain Medicine. 2001; 2(4):336-51

648. Macheridou A, Giannopoulou A, Karafotia A, Boutsikou M, Kaliviti I, Michaloliakou C. A randomized controlled trial of perioperative pregabalin administration for acute and chronic pain after radical modified mastectomy (RMM). European Journal of Anaesthesiology. 2012; 29(50):198

649. Macheridou A, Mihailidis M, Giannopoulou A, Vaivai A, Karafotia A, Michaloliakou C. A randomized controlled trial of preoperative administration of pregabalin for acute pain after radical modified mastectomy: 14AP3-6. European Journal of Anaesthesiology. 2011; 28(48):197

650. Macias A, Monedero P, Adame M, Torre W, Fidalgo I, Hidalgo F. A randomized, double-blinded comparison of thoracic epidural ropivacaine, ropivacaine/fentanyl, or bupivacaine/fentanyl for postthoracotomy analgesia. Anesthesia and Analgesia. 2002; 95(5):1344-50

651. MacKay IS, Ananian V. Analgesia following adult tonsillectomy: a comparative study of solpadeine and a soluble form of dextropropoxyphene napsylate and paracetamol. Journal of International Medical Research. 1982; 10(2):109-12

652. Madej TH, Wheatley RG, Jackson IJ, Hunter D. Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia. British Journal of Anaesthesia. 1992; 69(6):554-7

653. Madi-Jebara S, Adaimé C, Yazigi A, Haddad F, Hayek G, Sleilaty G et al. Thoracic epidural and intrathecal analgesia have similar effects on pain relief and respiratory function after thoracic surgery. Canadian Journal of Anesthesia. 2005; 52(7):710-716

654. Mahoney OM, Noble PC, Davidson J, Tullos HS. The effect of continuous epidural analgesia on postoperative pain, rehabilitation, and duration of hospitalization in total knee arthroplasty. Clinical Orthopaedics and Related Research. 1990; 260:30-37

655. Mahoori A, Noroozinia H, Hasani E, Hosainzadeh S. The effect of pre-operative administration of gabapentin on post-operative pain relief after herniorrhaphy. Saudi Journal of Anaesthesia. 2014; 8(2):220-3

656. Malan TP, Jr., Marsh G, Hakki SI, Grossman E, Traylor L, Hubbard RC. Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty. Anesthesiology. 2003; 98(4):950-6

657. Maleh PA, Alijanpour E, Nickbakhsh N, Modarress R, Naghshineh A, Esmaeili M. Effects of gabapentin on postoperative pain following laparoscopic cholecystectomy. Journal of mazandaran university of medical sciences. 2013; 23(103):29-32

658. Malmstrom K, Sapre A, Couglin H, Agrawal NG, Mazenko RS, Fricke JR, Jr. Etoricoxib in acute pain associated with dental surgery: a randomized, double-blind, placebo- and active comparator-controlled dose-ranging study. Clinical Therapeutics. 2004; 26(5):667-79

659. Mangano DT, Siliciano D, Hollenberg M, Leung JM, Browner WS, Goehner P et al. Postoperative myocardial ischemia: Therapeutic trials using intensive analgesia following surgery. Anesthesiology. 1992; 76(3):342-353

660. Manji M, Rigg C, Jones P, Ariffin S, Faroqui M. Tramadol for post operative analgesia in coronary artery bypass graft surgery. British Journal of Anaesthesia. 1997; 79(Suppl. 2):44

661. Mann C, Pouzeratte Y, Boccara G, Peccoux C, Vergne C, Brunat G et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. Anesthesiology. 2000; 92(2):433-41

662. Mannion S, O'Callaghan S, Murphy DB, Shorten GD. Tramadol as adjunct to psoas compartment block with levobupivacaine 0.5%: a randomized double-blinded study. British Journal of Anaesthesia. 2005; 94(3):352-6

663. Mansor SH, Choy CY. Effect of preoperative oral pregabalin on postoperative pain after mastectomy. Middle East Journal of Anesthesiology. 2015; 23(1):63-8

664. Manvelian G, Daniels S, Gibofsky A. A phase 2 study evaluating the efficacy and safety of a novel, proprietary, nano-formulated, lower dose oral diclofenac. Pain Medicine. 2012; 13(11):1491-8

665. Manyou B, Phupong V. Prospective randomized, double-blinded, placebo-controlled trial of preoperative etoricoxib for pain relief in uterine fractional curettage under paracervical block. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2008; 140(1):90-4

666. Mao Y, Wu L, Ding W. The efficacy of preoperative administration of gabapentin/pregabalin in improving pain after total hip arthroplasty: a meta-analysis. BMC Musculoskeletal Disorders. 2016; 17:373

667. Marappa P, Chikkapillappa MA, Chennappa NM, Pujari VS. A comparative study of analgesic efficacy of intrathecal buprenorphine with ultrasound-guided transversus abdominis plane block for postcesarean delivery analgesia. Anesthesia Essays and Researches. 2017; 11(2):376-379

668. Marashi SM, Morabi, Ali Akbar. The effect of pre-operative oral clonidine or gabapentin on post-operative pain intensity, morphine consumption and post-operative nausea and vomiting in patients who undergone thyroidectomy: A double-blind placebo-control study. Journal of Anesthesia & Clinical Research. 2012; 3:206

669. Mardani-Kivi M, Karimi Mobarakeh M, Haghighi M, Naderi-Nabi B, Sedighi-Nejad A, Hashemi-Motlagh K et al. Celecoxib as a pre-emptive analgesia after arthroscopic knee surgery; a triple-blinded randomized controlled trial. Archives of Orthopaedic and Trauma Surgery. 2013; 133(11):1561-6

670. Mardani-Kivi M, Karimi Mobarakeh M, Keyhani S, Haghighi M, Hashemi-Motlagh K, Saheb-Ekhtiari K. Arthroscopic bankart surgery: Does gabapentin reduce postoperative pain and opioid consumption? A triple-blinded randomized clinical trial. Orthopaedics & Traumatology, Surgery & Research. 2016; 102(5):549-53

671. Mardani-Kivi M, Mobarakeh MK, Keyhani S, Motlagh KH, Ekhtiari KS. Is gabapentin effective on pain management after arthroscopic anterior cruciate ligament reconstruction? A triple blinded randomized controlled trial. Archives of Bone & Joint Surgery. 2013; 1(1):18-22

672. Marret E, Remy C, Bonnet F, Postoperative Pain Forum G. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. British Journal of Surgery. 2007; 94(6):665-73

673. Martinez S, Alexander S. The effect of low-dose ketamine via patient-controlled analgesic pump on morphine consumption in the postoperative period in thoracotomies: a systematic review protocol. JBI Database Of Systematic Reviews And Implementation Reports. 2016; 14(8):34-42

674. Martinez V, Belbachir A, Jaber A, Cherif K, Jamal A, Ozier Y et al. The influence of timing of administration on the analgesic efficacy of parecoxib in orthopedic surgery. Anesthesia and Analgesia. 2007; 104(6):1521-7

675. Martinez V, Cymerman A, Ben Ammar S, Fiaud JF, Rapon C, Poindessous F et al. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study. Anaesthesia. 2014; 69(1):46-52

676. Massicotte L, Chalaoui KD, Beaulieu D, Roy JD, Bissonnette F. Comparison of spinal anesthesia with general anesthesia on morphine requirement after abdominal hysterectomy. Acta Anaesthesiologica Scandinavica. 2009; 53(5):641-7

677. Mathews TJ, Churchhouse AM, Housden T, Dunning J. Does adding ketamine to morphine patient-controlled analgesia safely improve post-thoracotomy pain? Interactive Cardiovascular and Thoracic Surgery. 2012; 14(2):194-9

678. Mathiesen O, Jacobsen LS, Holm HE, Randall S, Adamiec-Malmstroem L, Graungaard BK et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. British Journal of Anaesthesia. 2008; 101(4):535-41

679. Mathiesen O, Moiniche S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. BMC Anesthesiology. 2007; 7:6

680. Mathisen LC, Aasbo V, Raeder J. Lack of pre-emptive analgesic effect of (R)-ketamine in laparoscopic cholecystectomy. Acta Anaesthesiologica Scandinavica. 1999; 43(2):220-4

681. Mathisen LC, Skjelbred P, Skoglund LA, Oye I. Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. Pain. 1995; 61(2):215-220

682. Matsota P, Nakou M, Kalimeris K, Batistaki C, Pandazi A, Kostopanagiotou G. A single dose of celecoxib 200 mg improves postoperative analgesia provided via patient-controlled epidural technique after caesarean section. Archives of Medical Science. 2013; 9(5):877-82

683. Matsuda S. In Patients Having Hip or Knee Arthroplasty, Intravenous and Oral Acetaminophen Did Not Differ for 24-Hour Pain or Narcotic Use. Journal of Bone and Joint Surgery - American Volume. 2017; 99(16):1392

684. Matsunaga M, Dan K, Higa K. Epidural or intravenous buprenorphine for postoperative pain relief. Japanese Journal of Anesthesiology. 1984; 33(9):995-1002

685. Maurer K, Bonvini JM, Ekatodramis G, Serena S, Borgeat A. Continuous spinal anesthesia/analgesia vs. single-shot spinal anesthesia with patient-controlled analgesia for elective hip arthroplasty. Acta Anaesthesiologica Scandinavica. 2003; 47(7):878-83

686. Maurset A, Skoglund LA, Hustveit O, Oye I. Comparison of ketamine and pethidine in experimental and postoperative pain. Pain. 1989; 36(1):37-41

687. Mayo M, Gonzalez-Constan E, Gallego J, Bustos M, Pallares J. Comparative study of the analgesic effectiveness of tramadol versus morphine-metamizol after abdominal hysterectomy. Revista de la Sociedad Espanola del Dolor. 2003; 10(7):411-418

688. McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesthesia and Analgesia. 2004; 98(5):1385-400

689. McDonnell NJ, Paech MJ, Browning RM, Nathan EA. A randomised comparison of regular oral oxycodone and intrathecal morphine for post-caesarean analgesia. International Journal of Obstetric Anesthesia. 2010; 19(1):16-23

690. McKay WP, Donais P. Bowel function after bowel surgery: morphine with ketamine or placebo; a randomized controlled trial pilot study. Acta Anaesthesiologica Scandinavica. 2007; 51(9):1166-71

691. McNicol E, Ferguson M, Haroutounian S, Carr D, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD007126. DOI: 10.1002/14651858.CD007126.pub3.

692. McNicol E, Ferguson M, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD003348. DOI: 10.1002/14651858.CD003348.pub3.

693. McNicol ED, Ferguson MC, Schumann R. Single-dose intravenous diclofenac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD012498. DOI: 10.1002/14651858.CD012498.pub2.

694. McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiologica Scandinavica. 2014; 58(10):1199-213

695. McQuay HJ, Carroll D, Watts PG. Does adding small doses of codeine increase pain relief after third molar surgery? Clinical Journal of Pain. 1986; 2(3):197-201

696. McQuay HJ, Poon KH, Derry S, Moore RA. Acute pain: combination treatments and how we measure their efficacy. British Journal of Anaesthesia. 2008; 101(1):69-76

697. Mehlisch DR, Desjardins PJ, Daniels S, Hubbard RC. Single doses of parecoxib sodium intravenously are as effective as ketorolac in reducing pain after oral surgery. Journal of Oral and Maxillofacial Surgery. 2003; 61(9):1030-1037

698. Mehlisch DR, Desjardins PJ, Daniels S, Hubbard RC. The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. Journal of the American Dental Association. 2004; 135(11):1578-90

699. Mehta Y, Juneja R, Madhok H, Trehan N. Lumbar versus thoracic epidural buprenorphine for postoperative analgesia following coronary artery bypass graft surgery. Acta Anaesthesiologica Scandinavica. 1999; 43(4):388-93

700. Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. Journal of Critical Care. 2010; 25(3):458-462

701. Menda F, Koner O, Sayin M, Ergenoglu M, Kucukaksu S, Aykac B. Effects of single-dose gabapentin on postoperative pain and morphine consumption after cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2010; 24(5):808-13

702. Mendola C, Cammarota G, Netto R, Cecci G, Pisterna A, Ferrante D et al. S(+)-ketamine for control of perioperative pain and prevention of post thoracotomy pain syndrome: a randomized, double-blind study. Minerva Anestesiologica. 2012; 78(7):757-66

703. Meng Y, Jiang H, Zhang C, Zhao J, Wang C, Gao R et al. A comparison of the postoperative analgesic efficacy between epidural and intravenous analgesia in major spine surgery: a meta-analysis. Journal of Pain Research. 2017; 10:405-415

704. Menigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesthesia and Analgesia. 2005; 100(5):1394-9

705. Menigaux C, Fletcher D, Dupont X, Guignard B, Guirimand F, Chauvin M. The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. Anesthesia and Analgesia. 2000; 90(1):129-35

706. Menigaux C, Guignard B, Fletcher D, Sessler DI, Dupont X, Chauvin M. Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy. Anesthesia and Analgesia. 2001; 93(3):606-12

707. Menigaux C, Guignard B, Fletcher D, Sessler DI, Levron JC, Chauvin M. More epidural than intravenous sufentanil is required to provide comparable postoperative pain relief. Anesthesia and Analgesia. 2001; 93(2):472-6

708. Menkiti ID, Desalu I, Kushimo OT. Low-dose intravenous ketamine improves postoperative analgesia after caesarean delivery with spinal bupivacaine in African parturients. International Journal of Obstetric Anesthesia. 2012; 21(3):217-21

709. Mercadante S, Villari P, Casuccio A, Marrazzo A. A randomized-controlled study of intrathecal versus epidural thoracic analgesia in patients undergoing abdominal cancer surgery. Journal of Clinical Monitoring and Computing. 2008; 22(4):293-298

710. Mercanoglu E, Alanoglu Z, Ekmekci P, Demiralp S, Alkis N. Comparison of intravenous morphine, epidural morphine with/without bupivacaine or ropivacaine in postthoracotomy pain management with patient controlled analgesia technique. Brazilian Journal of Anesthesiology. 2013; 63(2):213-9

711. Mercieri M, Palmisani S, De Blasi RA, D'Andrilli A, Naccarato A, Silvestri B et al. Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial. British Journal of Anaesthesia. 2017; 119(4):792-802

712. Messenger DW, Murray HE, Dungey PE, van Vlymen J, Sivilotti ML. Subdissociative-dose ketamine versus fentanyl for analgesia during propofol procedural sedation: a randomized clinical trial. Academic Emergency Medicine. 2008; 15(10):877-86

713. Messina M, Boroli F, Landoni G, Bignami E, Dedola E, N'Zepa Batonga J et al. A comparison of epidural vs. paravertebral blockade in thoracic surgery. Minerva Anestesiologica. 2009; 75(11):616-21

714. Metry A, Ishak S, Khattab A. Does gabapentin have preemptive effects in women undergoing mastectomy? Acta Anaesthesiologica Italica. 2008; 59(1):62-76

715. Meunier A, Lisander B, Good L. Effects of celecoxib on blood loss, pain, and recovery of function after total knee replacement: a randomized placebo-controlled trial. Acta Orthopaedica. 2007; 78(5):661-7

716. Meurant F, Bodart A. Sparing analgesic effect using pregabaline in postsurgical trauma patients in the ICU. Critical Care. 2006; 10(Suppl 1):P439

717. Mezei M, Mihalik Z, Pénzes I. Continuous postoperative epidural analgesia in abdominal surgery using ropivacain. Magyar Sebeszet. 2002; 55(2):87-91

718. Mhuircheartaigh RJ, Moore RA, McQuay HJ. Analysis of individual patient data from clinical trials: epidural morphine for postoperative pain. British Journal of Anaesthesia. 2009; 103(6):874-81

719. Michelet P, Guervilly C, Helaine A, Avaro JP, Blayac D, Gaillat F et al. Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation. British Journal of Anaesthesia. 2007; 99(3):396-403

720. Mikkelsen S, Hilsted KL, Andersen PJ, Hjortso NC, Enggaard TP, Jorgensen DG et al. The effect of gabapentin on post-operative pain following tonsillectomy in adults. Acta Anaesthesiologica Scandinavica. 2006; 50(7):809-15

721. Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. American Journal of Emergency Medicine. 2015; 33(3):402-8

722. Mima T, Onchi H, Uchiyama S. Analgesic effects of pentazocine in postoperative pain. Japanese Journal of Anesthesiology. 1969; 18(4):299-304

723. Mishra A, Verma R, Bhatia VK, Chandra G, Gupta R, Chaudhary A. Thoracic paravertebral block for postoperative pain management in patients undergoing for nephrectomy: a randomised clinical trial. Journal of Clinical and Diagnostic Research. 2018; 12(10):UC05-UC08

724. Mishra R, Tripathi M, Chandola HC. Comparative clinical study of gabapentin and pregabalin for postoperative analgesia in laparoscopic cholecystectomy. Anesthesia Essays and Researches. 2016; 10(2):201-6

725. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. British Journal of Anaesthesia. 2015; 114(1):10-31

726. Misiran KB, Yahaya LS. The effectiveness of patient-controlled epidural analgesia with ropivacaine 0.165% with fentanyl 2.0 miroc g/ml or levobupivacaine 0.125% with fentanyl 2.0 micro g/ml as a method of postoperative analgesia after major orthopaedic surgery. Middle East Journal of Anesthesiology. 2013; 22(1):59-64

727. Mitra S, Ahuja V, Kaushik R. Comparative study of analgesic efficacy and tolerability of oral tapentadol-paracetamol combination vs. Oral tramadol-paracetamol combination for postoperative pain relief in patients undergoing hernia surgery. Acta Anaesthesiologica Belgica. 2017; 68(4):199-204

728. Mitsuhata H, Hirabayashi Y, Saitoh K, Horiguchi Y, Togashi H, Shimizu R et al. Patient-controlled analgesia with epidural pethidine or buprenorphine plus bupivacaine for postoperative analgesia. Japanese Journal of Anesthesiology. 1993; 42(11):1623-1627

729. Mitsuhata H, Kawakami T, Togashi H, Hirabayashi Y, Saitoh K, Fukuda H et al. The effects of continuous interpleural vs. epidural infusion for postoperative pain relief following thoracotomy. Japanese Journal of Anesthesiology. 1994; 43(10):1478-1485

730. Mitsuhata H, Matsumoto S, Hasegawa J, Ohtaka K. Continuous intravenous pethidine infusion for analgesia after upper abdominal surgery: a randomized, prospective double-blind comparison with continuous epidural infusion of pethidine. Japanese Journal of Anesthesiology. 1991; 40(12):1770-1776

731. Miziara LE, Simoni RF, Esteves LO, Cangiani LH, Grillo-Filho GF, Paula AG. Efficacy of Continuous S(+)-Ketamine Infusion for Postoperative Pain Control: A Randomized Placebo-Controlled Trial. Anesthesiology Research and Practice. 2016; 2016:6918327

732. Mizraji M. Clinical response to etodolac in the management of pain. European Journal of Rheumatology and Inflammation. 1990; 10(1):35-43

733. Modi MP, Shah VR. Epidural infusion of bupivacaine with morphine for pain relief after renal transplantation: a comparison with PCA intravenous morphine. Journal of Anaesthesiology, Clinical Pharmacology. 2009; 25(3):277-280

734. Modig J, Paalzow L. A comparison of epidural morphine and epidural bupivacaine for postoperative pain relief. Acta Anaesthesiologica Scandinavica. 1981; 25(5):437-41

735. Moghimi MH, Hosseini SN, Salehi V, Kamali K. The effects of oral pregabalin on post-Lichtenstein herniorrhaphic pain: a randomized clinical trial. Journal of Basic and Clinical Physiology and Pharmacology. 2018; 29(4):321-327

736. Mohamad MF, Mohammad MA, Hetta DF, Ahmed EH, Obiedallah AA, Elzohry AAM. Thoracic epidural analgesia reduces myocardial injury in ischemic patients undergoing major abdominal cancer surgery. Journal of Pain Research. 2017; 10:887-895

737. Mohammadi SS, Seyedi M. Effects of gabapentin on early postoperative pain, nausea and vomiting in laparoscopic surgery for assisted reproductive technologies. Pakistan Journal of Biological Sciences. 2008; 11(14):1878-80

738. Mohammed MH, Fahmy AM, Hakim KYK. Preoperative gabapentin augments intraoperative hypotension and reduces postoperative opioid requirements with functional endoscopic sinus surgery. Egyptian Journal of Anaesthesia. 2012; 28(3):189-192

739. Mohsin MU, Ahmed MJ, Shahid M, Furqan A. Effect of pre-emptive gabapentin on anaesthetic and analgesic requirements in patients undergoing rhinoplasty. Medical Forum Monthly. 2019; 30(3):95-99

740. Moll R, Derry S, Moore RA, McQuay HJ. Single dose oral mefenamic acid for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD007553. DOI: 10.1002/14651858.CD007553.pub2.

741. Moller PL, Sindet-Pedersen S, Petersen CT, Juhl GI, Dillenschneider A, Skoglund LA. Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery. British Journal of Anaesthesia. 2005; 94(5):642-8

742. Mondor ME, Massicotte L, Beaulieu D, Roy JD, Lapointe R, Dagenais M et al. Long-lasting analgesic effects of intraoperative thoracic epidural with bupivacaine for liver resection. Regional Anesthesia and Pain Medicine. 2010; 35(1):51-6

743. Monks DT, Hoppe DW, Downey K, Shah V, Bernstein P, Carvalho JC. A perioperative course of gabapentin does not produce a clinically meaningful improvement in analgesia after cesarean delivery: A randomized controlled trial. Anesthesiology. 2015; 123(2):320-6

744. Monrigal C, Jacob JP, Granry JC. Comparison of the analgesic efficacy of nalbuphine and its combination with propacetamol during the immediate postoperative period in gynecologic-obstetric surgery. Annales Françaises d'Anesthésie et de Réanimation. 1994; 13(2):153-157

745. Montazeri K, Kashefi P, Honarmand A. Pre-emptive gabapentin significantly reduces postoperative pain and morphine demand following lower extremity orthopaedic surgery. Singapore Medical Journal. 2007; 48(8):748-51

746. Montefiore A, Naffa I, Liu N, Bonnet F, Dupeyron JP, Lienhart A et al. Comparison of tramadol and dextropropoxyphene + paracetamol association in the treatment of post-operative pain. Therapie. 1991; 46(6):495

747. Mony D, Kulkarni D, Shetty L. Comparative evaluation of preemptive analgesic effect of injected intramuscular diclofenac and ketorolac after third molar surgery - a randomized controlled trial. Journal of Clinical and Diagnostic Research. 2016; 10(6):ZC102-ZC106

748. Moore R, Collins S, Edwards J, Derry S, McQuay H. Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative

pain. Cochrane Database of Systematic Reviews 1999, Issue 1. Art. No.: CD001440. DOI: 10.1002/14651858.CD001440.

749. Moore R, Derry S, Aldington D, Wiffen P. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD011407. DOI: 10.1002/14651858.CD011407.pub2.

750. Moore R, Derry S, Aldington D, Wiffen P. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD008659. DOI: 10.1002/14651858.CD008659.pub3.

751. Morad A, Winters B, Stevens R, White E, Weingart J, Yaster M et al. The efficacy of intravenous patient-controlled analgesia after intracranial surgery of the posterior fossa: a prospective, randomized controlled trial. Anesthesia and Analgesia. 2012; 114(2):416-23

752. Morad AH, Winters BD, Yaster M, Stevens RD, White ED, Thompson RE et al. Efficacy of intravenous patient-controlled analgesia after supratentorial intracranial surgery: a prospective randomized controlled trial. Clinical article. Journal of Neurosurgery. 2009; 111(2):343-350

753. Moradi-Farsani D, Hatami-Maskooni MR, Nazemolroaya B. Comparing the effects of fentanyl and sufentanil on hemodynamic parameters and acute pain intensity after deep vitrectomy surgery. Journal of Isfahan Medical School. 2018; 36(477):419-425

754. Moreira H, Jr., Moreira JP, Isaac RR, Alves-Neto O, Moreira TA, Vieira TH et al. Morphine spinal block anesthesia in patients who undergo an open hemorrhoidectomy: a prospective analysis of pain control and postoperative complications. Annals of Coloproctology. 2014; 30(3):135-40

755. Morgan SJ, Jeray KJ, Saliman LH, Miller HJ, Williams AE, Tanner SL et al. Continuous infusion of local anesthetic at iliac crest bone-graft sites for postoperative pain relief. A randomized, double-blind study. Journal of Bone & Joint Surgery - American Volume. 2006; 88(12):2606-12

756. Moro ET, Feitosa I, de Oliveira RG, Saraiva GFP, Rosalino R, Marossi VP et al. Ketamine does not enhance the quality of recovery following laparoscopic cholecystectomy: a randomized controlled trial. Acta Anaesthesiologica Scandinavica. 2017; 61(7):740-748

757. Morrow BC, Bunting H, Milligan KR. A comparison of diclofenac and ketorolac for postoperative analgesia following day-case arthroscopy of the knee joint. Anaesthesia. 1993; 48(7):585-7

758. Mortero RF, Clark LD, Tolan MM, Metz RJ, Tsueda K, Sheppard RA. The effects of small-dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. Anesthesia and Analgesia. 2001; 92(6):1465-9

759. Morue HI, Raj-Lawrence S, Saxena S, Delbaere A, Engelman E, Barvais LA. Placebo versus low-dose ketamine infusion in addition to remifentanil target-controlled infusion for conscious sedation during oocyte retrieval: A double-blinded, randomised controlled trial. European Journal of Anaesthesiology. 2018; 35(9):667-674

760. Moskovitz B, Bolkier M, Ginesin Y, Levin DR, Rosenberg B. Epidural morphine: a new approach to combined anesthesia and analgesia in urological patients. European Urology. 1986; 12(3):171-3

761. Moslemi F, Rasooli S, Baybordi A, Golzari SE. A comparison of patient controlled epidural analgesia with intravenous patient controlled analgesia for postoperative pain management after major gynecologic oncologic surgeries: A randomized controlled clinical trial. Anesthesiology & Pain Medicine. 2015; 5(5):e29540

762. Mostafa SF, Eid GM, Elkalla RS. Patient-controlled fascia iliaca compartment block versus fentanyl patient-controlled intravenous analgesia in patients undergoing femur fracture surgery. Egyptian Journal of Anaesthesia. 2018; 34(1):9-13

763. Mota FA, Marcolan JF, Pereira MH, Milanez AM, Dallan LA, Diccini S. Comparison study of two different patient-controlled anesthesia regiments after cardiac surgery. Revista Brasileira de Cirurgia Cardiovascular. 2010; 25(1):38-44

764. Motamed C, Bouaziz H, Franco D, Benhamou D. postoperative pain after low-dose intrathecal morphine in elective laparascopic cholecystectomy. British Journal of Anaesthesia. 1998; 80(Suppl 1):180

765. Motamed C, Spencer A, Farhat F, Bourgain JL, Lasser P, Jayr C. Postoperative hypoxaemia: continuous extradural infusion of bupivacaine and morphine vs patient-controlled analgesia with intravenous morphine. British Journal of Anaesthesia. 1998; 80(6):742-7

766. Motov S, Rockoff B, Cohen V, Pushkar I, Likourezos A, McKay C et al. Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: A randomized controlled trial. Annals of Emergency Medicine. 2015; 66(3):222-229 e1

767. Motov S, Rosenbaum S, Vilke GM, Nakajima Y. Is there a role for intravenous subdissociative-dose ketamine administered as an adjunct to opioids or as a single agent for acute pain management in the emergency department? Journal of Emergency Medicine. 2016; 51(6):752-757

768. Mourisse J, Hasenbos MA, Gielen MJ, Moll JE, Cromheecke GJ. Epidural bupivacaine, sufentanil or the combination for post-thoracotomy pain. Acta Anaesthesiologica Scandinavica. 1992; 36(1):70-4

769. Movafegh A, Ghafouri A, Nasr-Esfahani M, Gholamrezanezhad A, Madhkhan S. Post-thoracotomy analgesia--comparison epidural fentanyl to intravenous pethidine. Middle East Journal of Anesthesiology. 2007; 19(1):111-22

770. Moyse DW, Kaye AD, Diaz JH, Qadri MY, Lindsay D, Pyati S. Perioperative ketamine administration for thoracotomy pain. Pain Physician. 2017; 20(3):173-184

771. Mozell EJ, Sabanathan S, Mearns AJ, Bickford-Smith PJ, Majid MR, Zografos G. Continuous extrapleural intercostal nerve block after pleurectomy. Thorax. 1991; 46(1):21-4

772. Mu DL, Zhang DZ, Wang DX, Wang G, Li CJ, Meng ZT et al. Parecoxib supplementation to morphine analgesia decreases incidence of delirium in elderly patients after hip or knee replacement surgery: A randomized controlled trial. Anesthesia and Analgesia. 2017; 124(6):1992-2000

773. Mukherjee C, Koch E, Banusch J, Scholz M, Kaisers UX, Ender J. Intrathecal morphine is superior to intravenous PCA in patients undergoing minimally invasive cardiac surgery. Annals of Cardiac Anaesthesia. 2012; 15(2):122-7

774. Mukherjee M, Goswami A, Gupta SD, Sarbapalli D, Pal R, Kar S. Analgesia in post-thoracotomy patients: Comparison between thoracic epidural and thoracic paravertebral blocks. Anesthesia Essays and Researches. 2010; 4(2):75-80

775. Munteanu AM, Cionac Florescu S, Anastase DM, Stoica CI. Is there any analgesic benefit from preoperative vs. postoperative administration of etoricoxib in total knee arthroplasty under spinal anaesthesia?: A randomised double-blind placebo-controlled trial. European Journal of Anaesthesiology. 2016; 33(11):840-845

776. Murakami T, Okuda Y, Ishii M, Kobayashi A, Kawamura M. Comparison of intravenous fentanyl analgesia and epidural analgesia for postoperative pain relief. Japanese Journal of Anesthesiology. 2009; 58(9):1149-1153

777. Murdoch CJ, Crooks BA, Miller CD. Effect of the addition of ketamine to morphine in patient-controlled analgesia. Anaesthesia. 2002; 57(5):484-8

778. Murouchi T, Yamakage M. Retrolaminar block: analgesic efficacy and safety evaluation. Journal of Anesthesia. 2016; 30(6):1003-1007

779. Murphy DF, Graziotti P, Chalkiadis G, McKenna M. Patient-controlled analgesia: a comparison with nurse-controlled intravenous opioid infusions. Anaesthesia and Intensive Care. 1994; 22(5):589-92

780. Murthy GBN, Bengalorkar GM, Madhusudhana R. A comparative study of ketorolac with lornoxicam as pre-emptive analgesics in patients who were undergoing elective abdominal surgery under general anaesthesia. Journal of Clinical and Diagnostic Research. 2012; 6(3):418-422

781. Myhre M, Romundstad L, Stubhaug A. Pregabalin reduces opioid consumption and hyperalgesia but not pain intensity after laparoscopic donor nephrectomy. Acta Anaesthesiologica Scandinavica. 2017; 61(10):1314-1324

782. Nag S, Gode GR. Comparative evaluation of subarachnoid morphine & pethidine for post-operative analgesia. Indian Journal of Medical Research. 1984; 79:818-23

783. Najafi Anaraki A, Mirzaei K. The effect of gabapentin versus intrathecal fentanyl on postoperative pain and morphine consumption in cesarean delivery: a prospective, randomized, double-blind study. Archives of Gynecology and Obstetrics. 2014; 290(1):47-52

784. Nakhli MS, Kahloul M, Jebali C, Frigui W, Naija W. Effects of gabapentinoids premedication on shoulder pain and rehabilitation quality after laparoscopic cholecystectomy: Pregabalin versus gabapentin. Pain Research & Management. 2018; 2018:9834059

785. Nalini KB, Cherian A, Balachander H, Yashavantha Kumar C. Comparison of propofol and ketamine versus propofol and fentanyl for puerperal sterilization, a randomized clinical trial. Journal of Clinical and Diagnostic Research. 2014; 8(5):GC01-GC04

786. Nalini R, Ezhilramya J. A comparative study of efficacy and safety of lornoxicam and diclofenac as postoperative analgesics after mastoidectomy surgery. International Journal of Pharmacy and Pharmaceutical Sciences. 2017; 9(2):77-83

787. Nantha-Aree M, Paul J, Buckley N, Shahzad U, Cheng J, Thabane L et al. Gabapentin does not improve analgesia for total hip arthroplasty. Canadian Journal of Anesthesia. 2011; 58(1):S149

788. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual, updated 2018. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview

789. Navas J, Guadalix JI, Gil E, Gonzalez JM, Gomez ML, Munoz JL. Management of ortopaedic postoperative pain with morphine vs tramadol with i.v. continuous infusion pump plus PCA. Revista de la Sociedad Espanola del Dolor. 1996; 3(Suppl III):27-30

790. NCT. Clinical trial of gabapentin to improve postoperative pain in surgical patients. 2005. Available from: Https://clinicaltrials.gov/show/nct00221338 Last accessed: 09/11/2018

791. NCT. Pain treatment after total knee replacement - continuous epidural versus intravenous patient controlled analgesia with morphine. 2005. Available from: Https://clinicaltrials.gov/show/nct00270322 Last accessed: 07/11/2018

792. NCT. The use of ketamine as rescue analgesia in the recovery room following opioid administration. A double-blind randomised trial in postoperative patients. 2005. Available from: Https://clinicaltrials.gov/show/nct00163969 Last accessed: 09/11/18

793. NCT. Effect of perioperative i.v. low-dose S(+) ketamine. 2006. Available from: Https://clinicaltrials.gov/show/nct00354029 Last accessed: 09/11/18

794. NCT. Effects of nerve block on knee function after knee replacement. 2006. Available from: Https://clinicaltrials.gov/show/nct00358241 Last accessed: 07/11/2018

795. NCT. Oxycodone vs fentanyl for pain treatment after laparoscopic cholecystectomy. 2006. Available from: Https://clinicaltrials.gov/show/nct00369811 Last accessed: 07/11/2018

796. NCT. A pilot study of bupivacaine infusion in abdominal surgery. 2006. Available from: Https://clinicaltrials.gov/show/nct00280553 Last accessed: 07/11/2018

797. NCT. A study to evaluate the effectiveness and safety of tapentadol (CG5503) in the treatment of acute pain after hip replacement surgery compared with oxycodone and placebo followed by a voluntary open-label extension for safety. 2006. Available from: Https://clinicaltrials.gov/show/nct00364533 Last accessed: 12/11/2018

798. NCT. The effectiveness and safety of gabapentin for post-operative pain after cesarean section. 2007. Available from: Https://clinicaltrials.gov/show/nct00573664 Last accessed: 09/11/18

799. NCT. Efficacy and safety of pregabalin for pain following total knee replacement. 2007. Available from: Https://clinicaltrials.gov/show/nct00442546 Last accessed: 09/11/18

800. NCT. Gabapentin for postoperative pain management after cardiac surgery with median sternotomy. 2007. Available from: Https://clinicaltrials.gov/show/nct00572208 Last accessed: 09/11/18

801. NCT. Prospective, randomized controlled trial on perioperative pregabalin to reduce late-onset CRPS after TKA. 2007. Available from: Https://clinicaltrials.gov/show/nct00558753 Last accessed: 09/11/18

802. NCT. Role of pregabalin in treatment of post-op pain in fracture patients. 2007. Available from: Https://clinicaltrials.gov/show/nct00583869 Last accessed: 09/11/18

803. NCT. Study of the efficacy and safety of pregabalin compared to placebo for treatment of post-surgical pain from hysterectomy. 2007. Available from: Https://clinicaltrials.gov/show/nct00468845 Last accessed: 09/11/18

804. NCT. Surgical pain after inguinal hernia repair (SPAIHR). 2007. Available from: Https://clinicaltrials.gov/show/nct00551135 Last accessed: 09/11/18

805. NCT. Comparing 2 types of pain relief after cesarean delivery: Spinal morphine and tap block [NCT00799955]. 2008. Available from: Https://clinicaltrials.gov/show/nct00799955 Last accessed: 07/11/2018

806. NCT. Comparison of tramadol orally versus an optimized dose of intravenous tramadol for postoperative pain relief in ambulatory surgery. 2008. Available from: Https://clinicaltrials.gov/show/nct00735748 Last accessed: 12/11/2018

807. NCT. Continuous lumbar plexus block for postoperative pain control after total hip arthroplasty. 2008. Available from: Https://clinicaltrials.gov/show/nct00790179 Last accessed: 07/11/2018

808. NCT. Controlled-release oxycodone for postoperative analgesia after video-assisted thoracic surgery. 2008. Available from: Https://clinicaltrials.gov/show/nct00681174 Last accessed: 12/11/18

809. NCT. The effect of perioperative ketamine on acute and chronic pain after major back surgery. 2008. Available from: Https://clinicaltrials.gov/show/nct00618423 Last accessed: 09/11/18

810. NCT. The effects of peri-operative pregabalin administration on post-operative analgesia in patients undergoing coronary bypass grafting. 2008. Available from: Https://clinicaltrials.gov/show/nct00623285 Last accessed: 09/11/18

811. NCT. The effects of peri-operative pregabalin on post-operative pain following breast cancer surgery with axillary node dissection: A pilot study. 2008. Available from: Https://clinicaltrials.gov/show/nct00852683 Last accessed: 09/11/18

812. NCT. Lidocaine and ketamine versus standard care on acute and chronic pain. 2008. Available from: Https://clinicaltrials.gov/show/nct00720330 Last accessed: 09/11/18

813. NCT. Oral gabapentin versus placebo for treatment of postoperative pain following photorefractive keratectomy. 2008. Available from: Https://clinicaltrials.gov/show/nct00793910 Last accessed: 09/11/18

814. NCT. Perioperative pregabalin use, rehabilitation, pain outcomes and anxiety following hip surgery. 2008. Available from: Https://clinicaltrials.gov/show/nct00762099 Last accessed: 09/11/18

815. NCT. Perioperative use of gabapentin to decrease narcotic requirements in spinal fusion. 2008. Available from: Https://clinicaltrials.gov/show/nct00726999 Last accessed: 09/11/18

816. NCT. Post-operative pain scores and analgesic requirements after elective inguinal herniorrhaphy. 2008. Available from: Https://clinicaltrials.gov/show/nct00735124 Last accessed: 09/11/18

817. NCT. Pregabalin and orofacial neuropathic pain. 2008. Available from: Https://clinicaltrials.gov/show/nct00852436 Last accessed: 09/11/18

818. NCT. Pregabalin and post-thoracotomy pain. 2008. Available from: Https://clinicaltrials.gov/show/nct00663962 Last accessed: 09/11/18

819. NCT. Pregabalin for postoperative pain in women undergoing breast cancer surgery. 2008. Available from: Https://clinicaltrials.gov/show/nct00785382 Last accessed: 09/11/18

820. NCT. The role of intra-operative intracapsular blocks in post-operative pain management following total knee arthroplasty. 2008. Available from: Https://clinicaltrials.gov/show/nct00620828 Last accessed: 07/11/2018

821. NCT. Analgetic effect of preoperative pregabalin in patients undergoing nephrectomy. 2009. Available from: Https://clinicaltrials.gov/show/nct00957177 Last accessed: 09/11/18

822. NCT. Comparison of oral gabapentin and pregabalin in postoperative pain control after photorefractive keratectomy. 2009. Available from: Https://clinicaltrials.gov/show/nct00954187 Last accessed: 09/11/18

823. NCT. Does postoperative gabapentin reduce pain, opioid consumption and anxiety and have a positive effect on health related quality of life after radical prostatectomy? 2009. Available from: Https://clinicaltrials.gov/show/nct00982800 Last accessed: 09/11/18

824. NCT. Efficacy of gabapentin or amitriptyline to reduce postoperative pain after lumbar laminectomy and diskectomy. 2009. Available from: Https://clinicaltrials.gov/show/nct01014520 Last accessed: 09/11/18

825. NCT. Efficacy of perioperative pregabalin in reducing the incidence of chronic neuropathic pain and postthoracotomy syndrome. 2009. Available from: Https://clinicaltrials.gov/show/nct00967135 Last accessed: 09/11/18

826. NCT. Intra-operative ketamine infusions in opioid-dependent patients with chronic lower back pain. 2009. Available from: Https://clinicaltrials.gov/show/nct00899600 Last accessed: 09/11/18

827. NCT. Local anesthetic wound infusion and functional recovery after colon surgery. 2009. Available from: Https://clinicaltrials.gov/show/nct01062919 Last accessed: 07/11/2018

828. NCT. Morphine consumption in joint replacement patients, with and without gabapentin treatment, a randomized controlled study (MOBILE). 2009. Available from: Https://clinicaltrials.gov/show/nct00889148 Last accessed: 09/11/18

829. NCT. Study of the effect of the drug gabapentin on postoperative pain and incidence of postoperative nausea and vomiting. 2009. Available from: Https://clinicaltrials.gov/show/nct00886236 Last accessed: 09/11/18

830. NCT. Study to investigate the effectiveness of pregabalin for management of patients undergoing total hip replacement. 2009. Available from: Https://clinicaltrials.gov/show/nct00905437 Last accessed: 09/11/18

831. NCT. Analgesic effect of ketamine in patients undergoing hysteroscopic endometrial thermal ablation surgery. 2010. Available from: Https://clinicaltrials.gov/show/nct01106846 Last accessed: 20/06/2019

832. NCT. A comparison of pregabalin (Lyrica®) to placebo in pain relief after photorefractive keratectomy (PRK) surgery. 2010. Available from: Https://clinicaltrials.gov/show/nct01097577 Last accessed: 09/11/18

833. NCT. The effect of gabapentin on thoracic epidural analgesia following thoracotomy. 2010. Available from: Https://clinicaltrials.gov/show/nct01116583 Last accessed: 09/11/18

834. NCT. Efficacity, safety and cost of intravenous morphine titration alone or combined to ketamine. 2010. Available from: Https://clinicaltrials.gov/show/nct01146145 Last accessed: 09/11/18

835. NCT. Gabapentin for prophylaxis intrathecal morphine-induced pruritus. 2010. Available from: Https://clinicaltrials.gov/show/nct01236859 Last accessed: 09/11/18

836. NCT. Prevention of persistent postsurgical pain after thoracotomy. 2010. Available from: Https://clinicaltrials.gov/show/nct01243801 Last accessed: 09/11/18

837. NCT. The role of gabapentin in postoperative pain and epithelialization after photorefractive keratectomy. 2010. Available from: Https://clinicaltrials.gov/show/nct01177514 Last accessed: 09/11/18

838. NCT. Comparison between epidural and bilateral paravertebral blocks in liver resection. 2011. Available from: Https://clinicaltrials.gov/show/nct01407666 Last accessed: 07/11/2018

839. NCT. Effect of ketamine added to intravenous patient-controlled analgesia on postoperative pain, nausea and vomiting in patients undergoing lumbar spinal surgery. 2011. Available from: Https://clinicaltrials.gov/show/nct01394406 Last accessed: 09/11/18

840. NCT. Efficacy of pre-operative oral pregabalin in ambulatory inguinal hernia repair for post operative pain. 2011. Available from: Https://clinicaltrials.gov/show/nct01450345 Last accessed: 09/11/18

841. NCT. Postoperative pain and morphine consumption after mastectomy - Lyrica. 2011. Available from: Https://clinicaltrials.gov/show/nct01391858 Last accessed: 09/11/18

842. NCT. Spinal analgesia for colonic resection using an enhanced recovery after surgery (ERAS) program. 2011. Available from: Https://clinicaltrials.gov/show/nct01477190 Last accessed: 07/11/2018

843. NCT. The effects of continuous transversus abdominis plane (TAP) catheters on postoperative pain after renal transplantation. 2012. Available from: Https://clinicaltrials.gov/show/nct01679106 Last accessed: 07/11/2018

844. NCT. Efficacy of patient controlled epidural anesthesia versus continuous epidural analgesia for post-thoracotomy pain. 2012. Available from: Https://clinicaltrials.gov/show/nct01560429 Last accessed: 07/11/2018

845. NCT. Efficacy study of ketamine for postoperative pain in opioid dependent patients. 2012. Available from: Https://clinicaltrials.gov/show/nct01591382 Last accessed:

846. NCT. Pain control with total knee replacement. 2012. Available from: Https://clinicaltrials.gov/show/nct01680549 Last accessed: 09/11/18

847. NCT. TAP catheters versus intrathecal morphine for cesarean section. 2012. Available from: Https://clinicaltrials.gov/show/nct01593280 Last accessed: 07/11/2018

848. NCT. Does a perioperative course of gabapentin improve analgesia after cesarean delivery? 2013. Available from: Https://clinicaltrials.gov/show/nct01848119 Last accessed: 09/11/18

849. NCT. Epidural analgesia versus IV analgesia in lumbar spine fusions. 2013. Available from: Https://clinicaltrials.gov/show/nct01986946 Last accessed: 07/11/2018

850. NCT. Evaluation of preoperative use of pregabalin on postoperative analgesia after laparoscopic colorectal surgery. 2013. Available from: Https://clinicaltrials.gov/show/nct01940224 Last accessed: 09/11/18

851. NCT. Randomized study comparing the use of epidural analgesia to intravenous narcotics for laparoscopic colorectal resection. 2013. Available from: Https://clinicaltrials.gov/show/nct02086123 Last accessed: 07/11/2018

852. NCT. Transversus abdominis plane (TAP) block versus intrathecal morphine for caesarean section - randomised controlled trial. 2013. Available from: Https://clinicaltrials.gov/show/nct01931215 Last accessed: 07/11/2018

853. NCT. Assessing the efficacy of intravenous acetaminophen versus the oral formulation for perioperative pain treatment. 2014. Available from: Https://clinicaltrials.gov/show/nct02216682 Last accessed: 09/11/18

854. NCT. Comparison of efficacy of paravertebral and epidural analgesia after videothoracoscopic lung lobectomy. 2014. Available from: Https://clinicaltrials.gov/show/nct02040662 Last accessed: 07/11/2018

855. NCT. Effect of gabapentin on pain of the second cataract surgery. 2014. Available from: Https://clinicaltrials.gov/show/nct02127853 Last accessed: 09/11/18

856. NCT. Efficacy of IV acetaminophen for pain management. 2014. Available from: Https://clinicaltrials.gov/show/nct02028715 Last accessed: 09/11/18

857. NCT. PO vs. IV acetaminophen given perioperatively for 24 hr post-op pain control following total hip or knee replacement. 2014. Available from: Https://clinicaltrials.gov/show/nct02244619 Last accessed: 09/11/18

858. NCT. Pregabalin compared to gabapentin for pain control in lumbar disc surgery. 2014. Available from: Https://clinicaltrials.gov/show/nct02120703 Last accessed: 09/11/18

859. NCT. Prospective, randomized, double blind study comparing IV vs PO acetaminophen in patients undergoing lumbar discectomy. 2014. Available from: Https://clinicaltrials.gov/show/nct02067442 Last accessed: 09/11/18

860. NCT. Thoracic paravertebral blockade in video assisted thoracoscopic surgery (VATS). 2014. Available from: Https://clinicaltrials.gov/show/nct02302586 Last accessed: 07/11/2018

861. NCT. Administration of Pre-Operative Gabapentin to Patients Undergoing Laparoscopy. 2015. Available from: Https://clinicaltrials.gov/show/nct02359110 Last accessed: 09/11/18

862. NCT. Comparing ketamine and morphine in the treatment of acute fracture pain. 2015. Available from: Https://clinicaltrials.gov/show/nct02430818 Last accessed: 09/11/18

863. NCT. A comparison of intra-op ketamine vs placebo in patients having spinal fusion. 2015. Available from: Https://clinicaltrials.gov/show/nct02424591 Last accessed: 09/11/18

864. NCT. Efficacy of oral vs. intravenous acetaminophen. 2015. Available from: Https://clinicaltrials.gov/show/nct02643394 Last accessed: 09/11/18

865. NCT. Efficacy of S(+)-ketamine administered as a continuous infusion for the control of postoperative pain. 2015. Available from: Https://clinicaltrials.gov/show/nct02421913 Last accessed: 09/11/18

866. NCT. The impact of perioperative gabapentin on chronic groin pain after inguinal hernia repair. 2015. Available from: Https://clinicaltrials.gov/show/nct02419443 Last accessed: 09/11/18

867. NCT. Intravenous versus oral acetaminophen for postoperative pain control after cesarean delivery. 2015. Available from: Https://clinicaltrials.gov/show/nct02487303 Last accessed: 09/11/18

868. NCT. Ketamine combination with spinal morphine for post thoracic surgery pain : A randomized control study. 2015. Available from: Https://clinicaltrials.gov/show/nct02570230 Last accessed: 09/11/18

869. NCT. Ketamine in patients undergoing anterior cervical discectomy and fusion. 2015. Available from: Https://clinicaltrials.gov/show/nct02378740 Last accessed: 09/11/18

870. NCT. Spinal versus epidural analgesia in laparotomic liver surgery. 2015. Available from: Https://clinicaltrials.gov/show/nct02647047 Last accessed: 07/11/2018

871. NCT. Combination of preoperative gabapentin and tap blocks in decreasing postoperative pain. 2016. Available from: Https://clinicaltrials.gov/show/nct02927405 Last accessed: 09/11/18

872. NCT. Comparison of patient controlled & continuous epidural analgesia in thoraco-abdominal surgeries in cancer patients. 2016. Available from: Https://clinicaltrials.gov/show/nct02803385 Last accessed: 07/11/2018

873. NCT. Comparison of quadratus lumborum block with TAP block for postoperative analgesia after laparoscopic nephrectomy. 2016. Available from: Https://clinicaltrials.gov/show/nct02824939 Last accessed: 07/11/2018

874. NCT. Dose-response of ketamine in patient controlled analgesia in orthopaedic surgery patients. 2016. Available from: Https://clinicaltrials.gov/show/nct02994173 Last accessed: 09/11/18

875. NCT. Effects of continuous bilateral QL analgesia after open abdominal surgery. 2016. Available from: Https://clinicaltrials.gov/show/nct02684968 Last accessed: 07/11/2018

876. NCT. Epidural versus paravertebral block analgesia after hepatectomy. 2016. Available from: Https://clinicaltrials.gov/show/nct02909322 Last accessed: 07/11/2018

877. NCT. Gabapentin as a pre-emptive analgesic in oral and maxillofacial surgical procedures. 2016. Available from: Https://clinicaltrials.gov/show/nct02957097 Last accessed: 09/11/18

878. NCT. Intrathecal ketamine, morphine and both for lower abdominal cancer surgery pain. 2016. Available from: Https://clinicaltrials.gov/show/nct02726828 Last accessed: 09/11/18

879. NCT. Multicenter study to compare intravenous and oral acetaminophen for the treatment of acute moderate to severe pain. 2016. Available from: Https://clinicaltrials.gov/show/nct02746263 Last accessed: 09/11/18

880. NCT. Outcomes of perioperative pregabalin on total knee arthroplasty. 2016. Available from: Https://clinicaltrials.gov/show/nct02954484 Last accessed: 09/11/18

881. NCT. Preemptive and preventive use of paracetamol for pain relief after cesarean section. 2016. Available from: Https://clinicaltrials.gov/show/nct02714179 Last accessed: 09/11/18

882. NCT. A randomized controlled trial comparing intrathecal morphine with quadratus lumborum block for post-cesarean delivery analgesia. 2016. Available from: Https://clinicaltrials.gov/show/nct02871713 Last accessed: 07/11/2018

883. NCT. Single dose preoperative gabapentin use in minimally invasive hysterectomy for acute pain management. 2016. Available from: Https://clinicaltrials.gov/show/nct02703259 Last accessed: 09/11/18

884. NCT. Transversus abdominis plane block in iliac crest harvest-is it beneficial? 2016. Available from: Https://clinicaltrials.gov/show/nct02997124 Last accessed: 07/11/2018

885. NCT. Acetaminophen given per os and intravenous in sinus surgery. 2017. Available from: Https://clinicaltrials.gov/show/nct03295214 Last accessed: 09/11/18

886. NCT. Analgesia comparison of nalbuphine and morphine for laparoscopic myomectomy. 2017. Available from: Https://clinicaltrials.gov/show/nct03288428 Last accessed: 12/11/18

887. NCT. A comparison of ketamine infusion versus placebo in opioid tolerant and opioid naive patients after spinal fusion. 2017. Available from: Https://clinicaltrials.gov/show/nct03274453 Last accessed: 09/11/18

888. NCT. Effect of gabapentin on postoperative morphine consumption after sleeve gastrectomy. 2017. Available from: Https://clinicaltrials.gov/show/nct03023501 Last accessed: 09/11/18

889. NCT. The effectiveness of IV/PO acetaminophen in the perioperative period in reducing opiate use after lumbar spine fusion. 2017. Available from: Https://clinicaltrials.gov/show/nct03104816 Last accessed:

890. NCT. Efficacy of IV acetaminophen versus oral acetaminophen. 2017. Available from: Https://clinicaltrials.gov/show/nct03365622 Last accessed: 09/11/18

891. NCT. Epidural morphine for postoperative analgesia after total knee arthroplasty. 2017. Available from: Https://clinicaltrials.gov/show/nct03203967 Last accessed: 07/11/2018

892. NCT. Intraoperative low-dose ketamine infusion for patients with obstructive sleep apnea. 2017. Available from: Https://clinicaltrials.gov/show/nct03109418 Last accessed: 09/11/18

893. NCT. Intravenous ketamine and postoperative pain following cesarean section. 2017. Available from: Https://clinicaltrials.gov/show/nct03018301 Last accessed: 09/11/18

894. NCT. IV vs oral acetaminophen in spine fusion perioperative care. 2017. Available from: Https://clinicaltrials.gov/show/nct03020875 Last accessed: 09/11/18

895. NCT. Ketamine with multilevel paravertebral block for post video-assisted thoracic surgery pain. 2017. Available from: Https://clinicaltrials.gov/show/nct03280017 Last accessed: 09/11/18

896. NCT. Sedation methods during cataract surgery. 2017. Available from: Https://clinicaltrials.gov/show/nct03054103 Last accessed: 09/11/18

897. NCT. Transversus abdominis plane block versus spinal morphine after caesarean section : A comparison study. 2017. Available from: Https://clinicaltrials.gov/show/nct03263689 Last accessed: 07/11/2018

898. NCT. Ketamine for postoperative pain in bariatric surgery. 2018. Available from: Https://clinicaltrials.gov/show/nct03389022 Last accessed: 09/11/18

899. NCT. Perioperative ketamine for pain with gastric bypass. 2018. Available from: Https://clinicaltrials.gov/show/nct03448068 Last accessed: 09/11/18

900. NCT. Retrobulbar block versus ketamine infusion for post-enucleation analgesia. 2018. Available from: Https://clinicaltrials.gov/show/nct03507426 Last accessed: 09/11/18

901. NCT. Tramadol vs.tramadol with paracetamol. 2018. Available from: Https://clinicaltrials.gov/show/nct03482492 Last accessed: 09/11/18

902. Nendick M. Patient satisfaction with post-operative analgesia. Nursing Standard. 2000; 14(22):32-7

903. Nesek-Adam V, Grizelj-Stojcic E, Mrsic V, Rasic Z, Schwarz D. Preemptive use of diclofenac in combination with ketamine in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques. 2012; 22(3):232-8

904. Nesher N, Ekstein MP, Paz Y, Marouani N, Chazan S, Weinbroum AA. Morphine with adjuvant ketamine vs higher dose of morphine alone for immediate postthoracotomy analgesia. Chest. 2009; 136(1):245-252

905. Nesher N, Serovian I, Marouani N, Chazan S, Weinbroum AA. Ketamine spares morphine consumption after transthoracic lung and heart surgery without adverse hemodynamic effects. Pharmacological Research. 2008; 58(1):38-44

906. Nesioonpour S, Behaeen K. Effects of gabapentin on acute pain after nasal septoplasty. Otorinolaringologia. 2014; 64(2):65-9

907. Nessim A, Wexner SD, Agachan F, Alabaz O, Weiss EG, Nogueras JJ et al. Is bowel confinement necessary after anorectal reconstructive surgery? A prospective, randomized, surgeon-blinded trial. Diseases of the Colon and Rectum. 1999; 42(1):16-23

908. Neudecker J, Schwenk W, Junghans T, Pietsch S, Bohm B, Muller JM. Randomized controlled trial to examine the influence of thoracic epidural analgesia on postoperative ileus after laparoscopic sigmoid resection. British Journal of Surgery. 1999; 86(10):1292-5

909. Neuhauser C, Preiss V, Feurer MK, Muller M, Scholz S, Kwapisz M et al. Comparison of S-(+)-ketamine- with sufentanil-based anaesthesia for elective coronary artery bypass graft surgery: effect on troponin T levels. British Journal of Anaesthesia. 2008; 100(6):765-71

910. Ng A, Smith G, Davidson AC. Analgesic effects of parecoxib following total abdominal hysterectomy. British Journal of Anaesthesia. 2003; 90(6):746-9

911. Ng A, Swami A, Smith G, Emembolu J. Early analgesic effects of intravenous parecoxib and rectal diclofenac following laparoscopic sterilization: a double-blind, double-dummy randomized controlled trial. Journal of Opioid Management. 2008; 4(1):49-53

912. Ng A, Temple A, Smith G, Emembolu J. Early analgesic effects of parecoxib versus ketorolac following laparoscopic sterilization: a randomized controlled trial. British Journal of Anaesthesia. 2004; 92(6):846-9

913. Ng TT, Diamantaras D, Priestley J, Redman J, De Silva N, Mahanta V. Is celecoxib a useful adjunct in the treatment of post-tonsillectomy pain in the adult population? A randomised, double-blind, placebo-controlled study. Journal of Laryngology and Otology. 2017; 131(S1):S18-S28

914. Ng YT, Chen C, Chuah EC, Tan PP. The evaluation of subarachnoid administration of fentanyl for surgery and postoperative analgesia in patients undergoing cesarean section. Anaesthesiologica Sinica. 1990; 28(4):438-42

915. Ngan Kee WD, Ma ML, Gin T. Patient-controlled epidural analgesia after caesarean section using a disposable device. Australian and New Zealand Journal of Obstetrics and Gynaecology. 1997; 37(3):304-7

916. NHS Supply Chain Catalogue. NHS Supply Chain, 2018. Available from: https://my.supplychain.nhs.uk/catalogue

917. Nie JJ, Sun S, Huang SQ. Effect of oxycodone patient-controlled intravenous analgesia after cesarean section: a randomized controlled study. Journal of Pain Research. 2017; 10:2649-2655

918. Nielsen PT, Blom H, Nielsen SE. Less pain with epidural morphine after knee arthroplasty. Acta Orthopaedica Scandinavica. 1989; 60(4):447-8

919. Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Nikolajsen L, Dahl JB et al. Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. Pain. 2017; 158(3):463-470

920. Niemi L, Pitkanen M, Tuominen M, Rosenberg PH. Technical problems and side effects associated with continuous intrathecal or epidural post-operative analgesia in patients undergoing hip arthroplasty. European Journal of Anaesthesiology. 1994; 11(6):469-74

921. Niemi L, Tuominen M, Pitkanen M, Rosenberg PH. Comparison of parenteral diclofenac and ketoprofen for postoperative pain relief after maxillofacial surgery. Acta Anaesthesiologica Scandinavica. 1995; 39(1):96-9

922. Nightingale JJ, Knight MV, Higgins B, Dean T. Randomized, double-blind comparison of patient-controlled epidural infusion vs nurse-administered epidural infusion for postoperative analgesia in patients undergoing colonic resection. British Journal of Anaesthesia. 2007; 98(3):380-4

923. Nilsson E, Perttunen K, Kalso E. Intrathecal morphine for post-sternotomy pain in patients with myasthenia gravis: effects on respiratory function. Acta Anaesthesiologica Scandinavica. 1997; 41(5):549-56

924. Nimmaanrat S, Tangtrakulwanish B, Klabklay P, Boonriong T. Perioperative administration of pregabalin in patients undergoing arthroscopic anterior cruciate ligament reconstruction: does it help to relieve postoperative pain? Journal of the Medical Association of Thailand. 2012; 95(10):1297-301

925. Nishina K, Mikawa K, Shiga M, Takao Y, Maekawa N, Obara H. Diclofenac and flurbiprofen with or without clonidine for postoperative analgesia in children undergoing elective ophthalmological surgery. Paediatric Anaesthesia. 2000; 10(6):645-651

926. Nistal-Nuno B, Freire-Vila E, Castro-Seoane F, Camba-Rodriguez M. Preoperative low-dose ketamine has no preemptive analgesic effect in opioid-naive patients undergoing colon surgery when nitrous oxide is used - a randomized study [version 1; peer review: 2 approved]. F1000Research. 2014; 3:226

927. Nolan JP, Dow AA, Parr MJ, Dauphinee K, Kalish M. Patient-controlled epidural analgesia following post-traumatic pelvic reconstruction. A comparison with continuous epidural analgesia. Anaesthesia. 1992; 47(12):1037-41

928. Nourozi A, Talebi H, Fateh S, Mohammadzadeh A, Eghtesadi-Araghi P, Ahmadi Z et al. Effect of adding ketamine to pethidine on postoperative pain in patients undergoing major abdominal operations: a double blind randomized controlled trial. Pakistan Journal of Biological Sciences. 2010; 13(24):1214-8

929. O'Halloran P, Brown R. Patient-controlled analgesia compared with nurse-controlled infusion analgesia after heart surgery. Intensive and Critical Care Nursing. 1997; 13(3):126-9

930. O'Hara JF, Jr., Cywinski JB, Tetzlaff JE, Xu M, Gurd AR, Andrish JT. The effect of epidural vs intravenous analgesia for posterior spinal fusion surgery. Paediatric Anaesthesia. 2004; 14(12):1009-15

931. O'Neal JB, Freiberg AA, Yelle MD, Jiang Y, Zhang C, Gu Y et al. Intravenous vs oral acetaminophen as an adjunct to multimodal analgesia after total knee arthroplasty: a prospective, randomized, double-blind clinical trial. Journal of Arthroplasty. 2017; 32(10):3029-3033

932. Öğün C, Duman A, Ökesli S. The comparison of postoperative analgesic effects of preemptive ketamine and fentanyl use in mastectomy operations. The journal of the Turkish Society of Algology. 2001; 13(2):31-40

933. Oh JH, Seo HJ, Lee YH, Choi HY, Joung HY, Kim SH. Do selective COX-2 inhibitors affect pain control and healing after arthroscopic rotator cuff repair? A preliminary study. American Journal of Sports Medicine. 2018; 46(3):679-686

934. Oifa S, Sydoruk T, White I, Ekstein MP, Marouani N, Chazan S et al. Effects of intravenous patient-controlled analgesia with buprenorphine and morphine alone and in combination during the first 12 postoperative hours: a randomized, double-blind, four-arm trial in adults undergoing abdominal surgery. Clinical Therapeutics. 2009; 31(3):527-41

935. Okajima H, Tanaka O, Ushio M, Higuchi Y, Nagai Y, Iijima K et al. Ultrasound-guided continuous thoracic paravertebral block provides comparable analgesia and fewer episodes of hypotension than continuous epidural block after lung surgery. Journal of Anesthesia. 2015; 29(3):373-378

936. Oliashirazi A, Wilson-Byrne T, Shuler FD, Parvizi J. Patient-controlled fentanyl iontophoretic transdermal system improved postoperative mobility compared to intravenous patient-controlled analgesia morphine: A pooled analysis of randomized, controlled trials. Pain Practice. 2017; 17(2):197-207

937. Oliver WC, Jr., Nuttall GA, Murari T, Bauer LK, Johnsrud KH, Hall Long KJ et al. A prospective, randomized, double-blind trial of 3 regimens for sedation and analgesia after cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2011; 25(1):110-9

938. Olmedo-Gaya MV, Manzano-Moreno FJ, Galvez-Mateos R, Gonzalez-Rodriguez MP, Talero-Sevilla C, Vallecillo-Capilla M. Oral pregabalin for postoperative pain relief after third molar extraction: a randomized controlled clinical trial. Clinical Oral Investigations. 2016; 20(7):1819-26

939. Olmedo MV, Galvez R, Vallecillo M. Double-blind parallel comparison of multiple doses of ketorolac, ketoprofen and placebo administered orally to patients with postoperative dental pain. Pain. 2001; 90(1-2):135-41

940. Olson NZ, Otero AM, Marrero I, Tirado S, Cooper S, Doyle G et al. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. Journal of Clinical Pharmacology. 2001; 41(11):1238-47

941. Omar AAA, al Issa KA. Intravenous paracetamol (perfalgan) for analgesia after cesarean section: A double-blind randomized controlled study. Rawal Medical Journal. 2011; 36(4):267-268

942. Omar SH, Radwan KG, Youssif MA, Khafagy HF, Kamal NM, El-Sabae HH et al. A non opioid fast track anesthetic regimen for colonic resection. Journal of the Egyptian Society of Parasitology. 2009; 39(3):849-864

943. Omran AF, Mohamed AER. A randomized study of the effects of gabapentin versus placebo on post-thoracotomy pain and pulmonary function. Egyptian Journal of Anaesthesia. 2005; 21(4):277-281

944. Onal B, Akkaya T, Arik E, Gumus H. Effects of continuous spinal anesthesia and combined spinal-epidural anesthesia techniques on post-operative pain in total hip replacement patients. Anestezi Dergisi. 2007; 15(1):47-52

945. Ong CK, Lirk P, Tan JM, Sow BW. The analgesic efficacy of intravenous versus oral tramadol for preventing postoperative pain after third molar surgery. Journal of Oral and Maxillofacial Surgery. 2005; 63(8):1162-8

946. Ong EL, Osborne GA. Ketamine for co-induction of anaesthesia in oral surgery. Ambulatory Surgery. 2001; 9(3):131-135

947. Ong JC, Chin PL, Fook-Chong SM, Tang A, Yang KY, Tay BK. Continuous infiltration of local anaesthetic following total knee arthroplasty. Journal of Orthopaedic Surgery. 2010; 18(2):203-207

948. Owen H, Kluger MT, Ilsley AH, Baldwin AM, Fronsko RR, Plummer JL. The effect of fentanyl administered epidurally by patient-controlled analgesia, continuous infusion, or a combined technique of oxyhaemoglobin saturation after abdominal surgery. Anaesthesia. 1993; 48(1):20-5

949. Owen H, Plummer JL, Armstrong I, Mather LE, Cousins MJ. Variables of patient-controlled analgesia. 1. Bolus size. Anaesthesia. 1989; 44(1):7-10

950. Ozcan S, Inan N, Kaymak C, Unal N. The comparison of preemptive analgesic effectiveness of epidural and intravenous fentanil. Turkish Journal of Anaesthesiology and Reanimation. 2003; 31(6):290-295

951. Ozgencil E, Yalcin S, Tuna H, Yorukoglu D, Kecik Y. Perioperative administration of gabapentin 1,200 mg day-1 and pregabalin 300 mg day-1 for pain following lumbar laminectomy and discectomy: a randomised, double-blinded, placebo-controlled study. Singapore Medical Journal. 2011; 52(12):883-9

952. Ozgun S, Ugur B, Aydin ON, Eyigor H, Erpek G. The effect of preemptive ketamine on analgesia and analgesic consumption after tonsillectomy. Turkish Journal of Anaesthesiology and Reanimation. 2003; 31(5):247-252

953. Oztekin DS, Oztekin I, Issever H, Goksel O, Cinar B, Canik S. Postoperative effects of opioid analgesics administered via continuous perfusion and patient controlled analgesia after open heart surgery. Journal of the Pharmaceutical Society of Japan. 2006; 126(7):499-504

954. Öztürk T, Topcu İ, Yaldız S, Özbakkaloğlu A, Aşık K, Yentürk A. Comparison of thoracic epidural and paravertebral analgesia for postoperative pain control after thoracotomy. Agri. 2016; 28(1):32-38

955. Pacreu S, Fernandez Candil J, Molto L, Carazo J, Fernandez Galinski S. The perioperative combination of methadone and ketamine reduces post-operative opioid usage compared with methadone alone. Acta Anaesthesiologica Scandinavica. 2012; 56(10):1250-6

956. Paech MJ. Epidural pethidine or fentanyl during caesarean section: a double-blind comparison. Anaesthesia and Intensive Care. 1989; 17(2):157-65

957. Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. Anesthesia and Analgesia. 2007; 105(5):1449-53

958. Pagnoni B, Vignali M, Colella S, Monopoli R, Tiengo M. Comparative efficacy of oral ibuprofen arginine and intramuscular ketorolac in patients with postcaesarean section pain. Clinical Drug Investigation. 1996; 11(Suppl. 1):15-21

959. Palacios QT, Jones MM, Hawkins JL, Adenwala JN, Longmire S, Hess KR et al. Post-caesarean section analgesia: a comparison of epidural butorphanol and morphine. Canadian Journal of Anaesthesia. 1991; 38(1):24-30

960. Pan MH, Wei TT, Shieh BS. Comparative analgesic enhancement of alfentanil, fentanyl, and sufentanil to spinal tetracaine anesthesia for cesarean delivery. Acta Anaesthesiologica Sinica. 1994; 32(3):171-6

961. Pan PH, James CF. Anesthetic-postoperative morphine regimens for cesarean section and postoperative oxygen saturation monitored by a telemetric pulse oximetry network for 24 continuous hours. Journal of Clinical Anesthesia. 1994; 6(2):124-8

962. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. Journal of Neurosurgical Anesthesiology. 2005; 17(2):65-8

963. Pandey CK, Priye S, Ambesh SP, Singh S, Singh U, Singh PK. Prophylactic gabapentin for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. Journal of Postgraduate Medicine. 2006; 52(2):97-100

964. Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Canadian Journal of Anaesthesia. 2004; 51(4):358-63

965. Pandey CK, Sahay S, Gupta D, Ambesh SP, Singh RB, Raza M et al. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. Canadian Journal of Anaesthesia. 2004; 51(10):986-9

966. Pandey CK, Singhal V, Kumar M, Lakra A, Ranjan R, Pal R et al. Gabapentin provides effective postoperative analgesia whether administered pre-emptively or post-incision. Canadian Journal of Anaesthesia. 2005; 52(8):827-31

967. Pandit UA, Kothary SP, Pandit SK. Intravenous dezocine for postoperative pain: a double-blind, placebo-controlled comparison with morphine. Journal of Clinical Pharmacology. 1986; 26(4):275-80

968. Pang WW, Lei CH, Chang DP, Tung CC, Huang MH. The effects of tramadol versus fentanyl in attenuating hemodynamic response following tracheal intubation. Acta Anaesthesiologica Sinica. 1999; 37(4):191-6

969. Papadima A, Lagoudianakis EE, Antonakis PT, Pattas M, Kremastinou F, Katergiannakis V et al. Parecoxib vs. lornoxicam in the treatment of postoperative pain after laparoscopic cholecystectomy: a prospective randomized placebo-controlled trial. European Journal of Anaesthesiology. 2007; 24(2):154-8

970. Papaziogas B, Argiriadou H, Papagiannopoulou P, Pavlidis T, Georgiou M, Sfyra E et al. Preincisional intravenous low-dose ketamine and local infiltration with ropivacaine reduces postoperative pain after laparoscopic cholecystectomy. Surgical Endoscopy. 2001; 15(9):1030-3

971. Parbrook GD. Post-operative pain relief: comparison of methadone and morphine when used concurrently with nitrous-oxide analgesia. BMJ. 1966; 2(5514):616-8

972. Pareek A, Chandurkar N, Gupta A, Desai Y, Kumar SH, Swamy A et al. Comparative evaluation of efficacy and safety of etodolac and diclofenac sodium injection in patients with postoperative orthopedic pain. Current Medical Research and Opinion. 2011; 27(11):2107-15

973. Parikh B, Maliwad J, Shah VR. Preventive analgesia: effect of small dose of ketamine on morphine requirement after renal surgery. Journal of Anaesthesiology Clinical Pharmacology. 2011; 27(4):485-8

974. Parikh GP, Shah VR, Vora KS, Modi MP, Mehta T, Sonde S. Analgesic efficacy of peritubal infiltration of ropivacaine versus ropivacaine and morphine in percutaneous nephrolithotomy under ultrasonic guidance. Saudi Journal of Anaesthesia. 2013; 7(2):118-21

975. Park HS, Kim JH, Kim YJ, Kim DY. Plasma concentrations of morphine during postoperative pain control. Korean Journal of Pain. 2011; 24(3):146-153

976. Park IJ, Kim G, Ko G, Lee YJ, Hwang SH. Does preoperative administration of gabapentin/pregabalin improve postoperative nasal surgery pain? Laryngoscope. 2016; 126(10):2232-41

977. Park JS, Lee SG, Kim JI, Ban JS, Min BW. A comparison of thoracic versus lumbar epidural meperidine for analgesia after thoracotomy. Korean Journal of Anesthesiology. 1999; 37(3):453-458

978. Park JW, Kim JS, Han CS, Kim IH, Kim YJ, Kim CS. Comparison of midazolam-ketamine with midazolam for sedation during retrobulbar block in cataract surgery. Korean Journal of Anesthesiology. 1998; 34(6):1136-1143

979. Park SS, Kim DH, Nam IC, Lee IH, Hwang JW. The effectiveness of pregabalin for post-tonsillectomy pain control: a randomized controlled trial. PloS One. 2015; 10(2):e0117161

980. Park SY, An HS, Lee SH, Suh SW, Kim JL, Yoon SJ. A prospective randomized comparative study of postoperative pain control using an epidural catheter in patients undergoing posterior lumbar interbody fusion. European Spine Journal. 2016; 25(5):1601-1607

981. Park YB, Ha CW, Cho SD, Lee MC, Lee JH, Seo SS et al. A randomized study to compare the efficacy and safety of extended-release and immediate-release tramadol HCl/acetaminophen in patients with acute pain following total knee replacement. Current Medical Research and Opinion. 2015; 31(1):75-84

982. Park YJ, Chung MH. Analgesia after arthroscopic shoulder surgery: Study of effective concentration of continuous patient-controlled subacromial ropivacaine infusion. Korean Journal of Anesthesiology. 2006; 50(5):552-556

983. Parker RK, Holtmann B, White PF. Patient-controlled analgesia. Does a concurrent opioid infusion improve pain management after surgery? JAMA. 1991; 266(14):1947-52

984. Parker RK, White PF. Epidural patient-controlled analgesia: an alternative to intravenous patient-controlled analgesia for pain relief after cesarean delivery. Anesthesia and Analgesia. 1992; 75(2):245-51

985. Parkhouse J, Mariott G. Forum. Postoperative analgesia with ketamine and pethidine. Anaesthesia. 1977; 32(3):285-289

986. Parsa AA, Soon CW, Parsa FD. The use of celecoxib for reduction of pain after subpectoral breast augmentation. Aesthetic Plastic Surgery. 2005; 29(6):441-4; discussion 445

987. Parveen S, Negi DS, Kumar R, Bagwan MC. Oral clonidine vs oral pregabalin premedication to attenuate pressor response to direct laryngoscopy in patients undergoing laparoscopic cholecystectomy: a randomized double blind study. Journal of Clinical and Diagnostic Research. 2016; 10(9):UC21-UC25

988. Patrick JA, Meyer-Witting M, Reynolds F. Lumbar epidural diamorphine following thoracic surgery. A comparison of infusion and bolus administration. Anaesthesia. 1991; 46(2):85-9

989. Patrocinio LG, Rangel Mde O, Marques Miziara GS, Rodrigues AM, Patrocinio JA, Patrocinio TG. A comparative study between ketorolac and ketoprofen in postoperative pain after uvulopalatopharyngoplasty. Revista Brasileira de Otorrinolaringologia. 2007; 73(3):339-42

990. Paulsen EK, Porter MG, Helmer SD, Linhardt PW, Kliewer ML. Thoracic epidural versus patient-controlled analgesia in elective bowel resections. American Journal of Surgery. 2001; 182(6):570-7

991. Pavlidis T, Papaziogas B, Souparis A, Patsas A, Koutelidakis I, Papaziogas T. Modern stapled Longo procedure vs. conventional Milligan-Morgan hemorrhoidectomy: a randomized controlled trial. International Journal of Colorectal Disease. 2002; 17(1):50-3

992. Pendi A, Field R, Farhan SD, Eichler M, Bederman SS. Perioperative ketamine for analgesia in spine surgery: A meta-analysis of randomized controlled trials. Spine. 2018; 43(5):E299-E307

993. Peng PW, Li C, Farcas E, Haley A, Wong W, Bender J et al. Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. British Journal of Anaesthesia. 2010; 105(2):155-61

994. Peng PW, Wijeysundera DN, Li CC. Use of gabapentin for perioperative pain control -- a meta-analysis. Pain Research & Management. 2007; 12(2):85-92

995. Pereira VBP, Garcia R, Torricelli AAM, Mukai A, Bechara SJ. Codeine plus acetaminophen for pain after photorefractive keratectomy: A randomized, double-blind, placebo-controlled add-on trial. Cornea. 2017; 36(10):1206-1212

996. Perrin SB, Purcell AN. Intraoperative ketamine may influence persistent pain following knee arthroplasty under combined general and spinal anaesthesia: a pilot study. Anaesthesia and Intensive Care. 2009; 37(2):248-53

997. Perttunen K, Nilsson E, Kalso E. I.V. diclofenac and ketorolac for pain after thoracoscopic surgery. British Journal of Anaesthesia. 1999; 82(2):221-7

998. Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P et al. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. British Journal of Anaesthesia. 2011; 106(6):873-81

999. Pettersson PH, Lindskog EA, Owall A. Patient-controlled versus nurse-controlled pain treatment after coronary artery bypass surgery. Acta Anaesthesiologica Scandinavica. 2000; 44(1):43-7

1000. Petti A. Postoperative pain relief with pentazocine and acetaminophen: comparison with other analgesic combinations and placebo. Clinical Therapeutics. 1985; 8(1):126-33

1001. Peyton PJ, Myles PS, Silbert BS, Rigg JA, Jamrozik K, Parsons R. Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. Anesthesia and Analgesia. 2003; 96(2):548-554

1002. Phaphak W. The comparative study of the holistic service of anesthesia for gynecological surgery at Chon Buri Cancer Center. Chon Buri Hospital Journal. 2003; 28(3):157-162

1003. Phillips DM, Moore RA, Bullingham RE, Allen MC, Baldwin D, Fisher A et al. Plasma morphine concentrations and clinical effects after thoracic extradural morphine or diamorphine. British Journal of Anaesthesia. 1984; 56(8):829-36

1004. Phinchantra P, Bunyavehchevin S, Suwajanakorn S, Wisawasukmongchol W. The preemptive analgesic effect of celecoxib for day-case diagnostic laparoscopy. Journal of the Medical Association of Thailand. 2004; 87(3):283-8

1005. Phittayawechwiwat W, Thanantaseth C, Ayudhya NI, P OP, Kongprasert J. Oral etoricoxib for pain relief during fractional curettage: a randomized controlled trial. Journal of the Medical Association of Thailand. 2007; 90(6):1053-7

1006. Pintaric TS, Potocnik I, Hadzic A, Stupnik T, Pintaric M, Novak Jankovic V. Comparison of continuous thoracic epidural with paravertebral block on perioperative analgesia and hemodynamic stability in patients having open lung surgery. Regional Anesthesia and Pain Medicine. 2011; 36(3):256-60

1007. Plunkett A, Haley C, McCoart A, Beltran T, Highland KB, Berry-Caban C et al. A preliminary examination of the comparative efficacy of intravenous vs oral acetaminophen in the treatment of perioperative pain. Pain Medicine. 2017; 18(12):2466-2473

1008. Polat O, Karaman AI, Durmus E. Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain. Angle Orthodontist. 2005; 75(5):791-6

1009. Politi JR, Davis RL, 2nd, Matrka AK. Randomized prospective trial comparing the use of intravenous versus oral acetaminophen in total joint arthroplasty. Journal of Arthroplasty. 2017; 32(4):1125-1127

1010. Poon KH, Tan KH, Ho KY. Efficacy of fentanyl iontophoretic transdermal system in postoperative pain-A meta-analysis. Acute Pain. 2009; 11(2):65-74

1011. Popping DM, Elia N, Marret E, Remy C, Tramer MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Archives of Surgery. 2008; 143(10):990-9; discussion 1000

1012. Popping DM, Elia N, Marret E, Wenk M, Tramer MR. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomized trials. Pain. 2012; 153(4):784-93

1013. Pourfakhr P, Khajavi MR, Jalali A, Memari F, Etezadi F, Momeni Roochi M et al. Low-dose preoperative pregabalin improves postoperative pain management in septorhinoplasty surgery: A double-blind randomized clinical trial. European Archives of Oto-Rhino-Laryngology. 2019; 276(8):2243-2249

1014. Poyhia R, Hynynen M, Seppala T, Roine RO, Verkkala K, Olkkola KT. Pharmacodynamics and pharmacokinetics of high-dose oxycodone infusion during

and after coronary artery bypass grafting. Journal of Cardiothoracic and Vascular Anesthesia. 2004; 18(6):748-54

1015. Poylin V, Quinn J, Messer K, Nagle D. Gabapentin significantly decreases posthemorrhoidectomy pain: a prospective study. International Journal of Colorectal Disease. 2014; 29(12):1565-9

1016. Prasartritha T, Kunakornsawat S, Tungsiripat R, Jampa J, Throngnumchai R. A prospective randomized trial comparing epidural morphine through intraoperatively placed epidural catheter and intravenous morphine in major lumbar spinal surgery. Journal of Spinal Disorders & Techniques. 2010; 23(8):e43-e46

1017. Priestley MC, Cope L, Halliwell R, Gibson P, Chard RB, Skinner M et al. Thoracic epidural anesthesia for cardiac surgery: the effects on tracheal intubation time and length of hospital stay. Anesthesia and Analgesia. 2002; 94(2):275-82

1018. Prieto-Alvarez P, Tello-Galindo I, Cuenca-Pena J, Rull-Bartomeu M, Gomar-Sancho C. Continuous epidural infusion of racemic methadone results in effective postoperative analgesia and low plasma concentrations. Canadian Journal of Anaesthesia. 2002; 49(1):25-31

1019. Puolakka PA, Puura AI, Pirhonen RA, Ranta AU, Autio V, Lindgren L et al. Lack of analgesic effect of parecoxib following laparoscopic cholecystectomy. Acta Anaesthesiologica Scandinavica. 2006; 50(8):1027-32

1020. Puura A, Puolakka P, Rorarius M, Salmelin R, Lindgren L. Etoricoxib pre-medication for post-operative pain after laparoscopic cholecystectomy. Acta Anaesthesiologica Scandinavica. 2006; 50(6):688-93

1021. Qadeer M, Waqas M, Rashid MJ, Enam SA, Sharif S, Murtaza G. Preventive gabapentin versus pregabalin to decrease postoperative pain after lumbar microdiscectomy: A randomized controlled trial. Asian Spine Journal. 2017; 11(1):93-98

1022. Qi Y, Yao X, Zhang B, Du X. Comparison of recovery effect for sufentanil and remifentanil anesthesia with TCI in laparoscopic radical resection during colorectal cancer. Oncology Letters. 2016; 11(5):3361-3365

1023. Rabinov M, Rosenfeldt FL, McLean AJ. A double-blind comparison of the relative efficacy, side effects and cost of buprenorphine and morphine in patients after cardiac surgery. Australian and New Zealand Journal of Surgery. 1987; 57(4):227-31

1024. Radhakrishnan M, Bithal PK, Chaturvedi A. Effect of preemptive gabapentin on postoperative pain relief and morphine consumption following lumbar laminectomy and discectomy: a randomized, double-blinded, placebo-controlled study. Journal of Neurosurgical Anesthesiology. 2005; 17(3):125-8

1025. Radovanovic D, Radovanovic Z, Skoric-Jokic S, Tatic M, Mandic A, Ivkovic-Kapicl T. Thoracic epidural versus intravenous patient-controlled analgesia after open colorectal cancer surgery. Acta Clinica Croatica. 2017; 56(2):244-254

1026. Radpay B, Karimi-Zandi S, Dabir S, Parsa T. Comparison between epidural morphine versus morphine + fentanyl in lung resection surgery. Archives of Iranian Medicine. 2003; 6(2):81-85

1027. Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, Eloy JD. Role of ketamine in acute postoperative pain management: a narrative review. BioMed Research International. 2015; 2015:749837

1028. Radwan K, Youssef M, Tawdy A, Ali M, Kamal N. Melatonin versus gabapentin. A comparative study as preemptive medications. The Internet Journal of Anesthesiology. 2010; 23(1)

1029. Raffa RB, Pawasauskas J, Pergolizzi JV, Jr., Lu L, Chen Y, Wu S et al. Pharmacokinetics of oral and intravenous paracetamol (acetaminophen) when co-administered with intravenous morphine in healthy adult subjects. Clinical Drug Investigation. 2018; 38(3):259-268

1030. Rafiq S, Steinbruchel DA, Wanscher MJ, Andersen LW, Navne A, Lilleoer NB et al. Multimodal analgesia versus traditional opiate based analgesia after cardiac surgery, a randomized controlled trial. Journal of Cardiothoracic Surgery. 2014; 9:52

1031. Rahimi M, Honarmand A, Naderi F, Safavi SMR, Heidari SM. Effects of adding low-dose ketamine to remifentanil-midazolam infusion under topical anesthesia on pain relief after nasal bone fracture. Journal of Isfahan Medical School. 2012; 30(198)

1032. Rai AS, Khan JS, Dhaliwal J, Busse JW, Choi S, Devereaux PJ et al. Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients undergoing breast cancer surgery: a systematic review and meta-analysis of randomized controlled trials. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2017; 70(10):1317-1328

1033. Ram DB, Khanna DR, Kumar DM, Tiwary DPK, Suwalka DU. Pre-emptive gabapentin v/s pregabalin for acute postoperative analgesia following abdominal hysterectomy under spinal anaesthesia: A randomized double blind study. Southeast Asian Journal of Case Report and Review. 2015; 4(5):2031-2039

1034. Rao SM, Netke B, Ponavala T, Kumar S, Dharmarakshak A. Post-operative pain relief by PCA v/s oral tramadol in cardiac surgery. Annals of Cardiac Anaesthesia. 2001; 4(1):13-16

1035. Rapchuk IL, O'Connell L, Liessmann CD, Cornelissen HR, Fraser JF. Effect of gabapentin on pain after cardiac surgery: a randomised, double-blind, placebo-controlled trial. Anaesthesia and Intensive Care. 2010; 38(3):445-51

1036. Rascon-Martinez DM, Guzman-Sanchez JA, Corral-Urdapilleta NP, Arguelles-Uribe GD, Velazquez-Loeza J, Soto-Palma G et al. Gabapentin at a dose of 300 vs. 450 mg as an anesthetic premedication for reactive hypertension, anxiety and analgesia. Gaceta Medica de México. 2018; 154(1):54-61

1037. Rascón-Martínez DM, Guzmán-Sánchez JA, Corral-Urdapilleta NP, Arguelles-Uribe GD, Velázquez-Loeza J, Soto-Palma G et al. Gabapentine 300 mg vs. 450 mg as anesthetic premedication for reactive hypertension, anxiety and analgesia. Gaceta Medica de México. 2018; 154(1):54-61

1038. Rasmussen GL, Malmstrom K, Bourne MH, Jove M, Rhondeau SM, Kotey P et al. Etoricoxib provides analgesic efficacy to patients after knee or hip replacement surgery: a randomized, double-blind, placebo-controlled study. Anesthesia and Analgesia. 2005; 101(4):1104-11

1039. Rasmussen LA, Ryhammer PK, Greisen J, Bhavsar RR, Lorentzen AG, Jakobsen CJ. Ultrashort acting remifentanil is not superior to long-acting sufentanil in preserving cognitive function-a randomized study. Journal of Clinical Anesthesia. 2016; 33:127-34

1040. Ratchanon S, Phaloprakarn C, Traipak K. Pain control in laparoscopic gynecologic surgery with/without preoperative (preemptive) parecoxib sodium injection: a

randomized study. Journal of the Medical Association of Thailand. 2011; 94(10):1164-8

1041. Rauck RL, Raj PP, Knarr DC, Denson DD, Speight KL. Comparison of the efficacy of epidural morphine given by intermittent injection or continuous infusion for the management of postoperative pain. Regional Anesthesia. 1994; 19(5):316-24

1042. Rawal N. Epidural and spinal agents for postoperative analgesia. Surgical Clinics of North America. 1999; 79(2):313-44

1043. Rawal N, Allvin R, Amilon A, Ohlsson T, Hallen J. Postoperative analgesia at home after ambulatory hand surgery: a controlled comparison of tramadol, metamizol, and paracetamol. Anesthesia and Analgesia. 2001; 92(2):347-51

1044. Rawal N, Gupta A, Helsing M, Grell K, Allvin R. Pain relief following breast augmentation surgery: a comparison between incisional patient-controlled regional analgesia and traditional oral analgesia. European Journal of Anaesthesiology. 2006; 23(12):1010-7

1045. Rawal N, Macquaire V, Catala E, Berti M, Costa R, Wietlisbach M. Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: a double-blind, double-dummy, randomized, parallel-group trial. Journal of Pain Research. 2011; 4:103-10

1046. Rawal N, Van Zimdert A, Holmstrom B, Crowhurst JA. Combined spinal-epidural technique. Regional Anesthesia. 1997; 22(5):406-423

1047. Rawal N, Viscusi E, Peloso PM, Minkowitz HS, Chen L, Shah S et al. Evaluation of etoricoxib in patients undergoing total knee replacement surgery in a double-blind, randomized controlled trial. BMC Musculoskeletal Disorders. 2013; 14:300

1048. Recart A, Issioui T, White PF, Klein K, Watcha MF, Stool L et al. The efficacy of celecoxib premedication on postoperative pain and recovery times after ambulatory surgery: a dose-ranging study. Anesthesia and Analgesia. 2003; 96(6):1631-5

1049. Reeves M, Lindholm DE, Myles PS, Fletcher H, Hunt JO. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blinded, randomized controlled trial. Anesthesia and Analgesia. 2001; 93(1):116-20

1050. Remerand F, Le Tendre C, Baud A, Couvret C, Pourrat X, Favard L et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesthesia and Analgesia. 2009; 109(6):1963-71

1051. Renner B, Zacher J, Buvanendran A, Walter G, Strauss J, Brune K. Absorption and distribution of etoricoxib in plasma, CSF, and wound tissue in patients following hip surgery--a pilot study. Naunyn-Schmiedebergs Archives of Pharmacology. 2010; 381(2):127-36

1052. Reuben SS, Buvenandran A, Katz B, Kroin JS. A prospective randomized trial on the role of perioperative celecoxib administration for total knee arthroplasty: improving clinical outcomes.[Retraction in Shafer SL. Anesth Analg. 2009 Apr;108(4):1350; PMID: 19299812]. Anesthesia and Analgesia. 2008; 106(4):1258-64

1053. Reuben SS, Ekman EF. The effect of cyclooxygenase-2 inhibition on analgesia and spinal fusion. Journal of Bone & Joint Surgery - American Volume. 2005; 87(3):536-42

1054. Reuben SS, Ekman EF, Charron D. Evaluating the analgesic efficacy of administering celecoxib as a component of multimodal analgesia for outpatient anterior cruciate ligament reconstruction surgery. Anesthesia and Analgesia. 2007; 105(1):222-7

1055. Reyes-Perez RA, Juarez-Pichardo JS, de los Rios-Soriano G. Comparison of pregabalin and gabapentin in perioperative of laparoscopic cholecystectomy. Revista Mexicana de Anestesiologia. 2017; 40(1):8-13

1056. Reza FM, Zahra F, Esmaeel F, Hossein A. Preemptive analgesic effect of ketamine in patients undergoing elective cesarean section. Clinical Journal of Pain. 2010; 26(3):223-6

1057. Rezaeian A. Administering of pregabalin and acetaminophen on management of postoperative pain in patients with nasal polyposis undergoing functional endoscopic sinus surgery. Acta Oto-Laryngologica. 2017; 137(12):1249-1252

1058. Richards P, Riff D, Kelen R, Stern W. A phase 3, randomized, double-blind comparison of analgesic efficacy and tolerability of Q8003 vs oxycodone or morphine for moderate-to-severe postoperative pain following bunionectomy surgery. Pain Medicine. 2013; 14(8):1230-8

1059. Richards P, Riff D, Kelen R, Stern W, MoxDuo Study T. Analgesic and adverse effects of a fixed-ratio morphine-oxycodone combination (MoxDuo) in the treatment of postoperative pain. Journal of Opioid Management. 2011; 7(3):217-28

1060. Richardson L, Dunning J, Hunter S. Is intrathecal morphine of benefit to patients undergoing cardiac surgery. Interactive Cardiovascular and Thoracic Surgery. 2009; 8(1):117-122

1061. Rimaitis K, Pavalkis D. Does epidural anaesthesia and analgesia really improves surgical outcome after colorectal cancer surgery? Acta Chirurgica Iugoslavica. 2006; 53(2):85-9

1062. Rimaz S, Heirati A, Nabi BN, Sedighinejad A, Ashraf A, Alavi E. Pre-emptive gabapentin versus pregabalin for acute postoperative pain after external dacryocystorhinostomy surgery under regional anesthesia: A randomized placebo-controlled trial. Nautilus. 2014; 128(1):43-51

1063. Robinson CY, Rubino CM, Farr SJ. A pharmacokinetic evaluation of single and multiple doses of extended-release hydrocodone bitartrate in subjects experiencing surgical or osteoarthritic pain. Journal of Opioid Management. 2015; 11(5):405-415

1064. Roediger L, Joris J, Senard M, Larbuisson R, Canivet JL, Lamy M. The use of pre-operative intrathecal morphine for analgesia following coronary artery bypass surgery. Anaesthesia. 2006; 61(9):838-44

1065. Roelofse JA, van der Bijl P, Joubert JJ. An open comparative study of the analgesic effects of tenoxicam and diclofenac sodium after third molar surgery. Anesthesia and Pain Control in Dentistry. 1993; 2(4):217-22

1066. Roelofse JA, Van der Bijl P, Joubert JJ. Analgesic and anti-inflammatory efficacy of tenoxicam and diclofenac sodium after third molar surgery. Anesthesia Progress. 1996; 43(4):103-7

1067. Rorarius MG, Mennander S, Suominen P, Rintala S, Puura A, Pirhonen R et al. Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. Pain. 2004; 110(1-2):175-81

1068. Rorarius MG, Suominen P, Baer GA, Romppanen O, Tuimala R. Diclofenac and ketoprofen for pain treatment after elective caesarean section. British Journal of Anaesthesia. 1993; 70(3):293-7

1069. Rosaeg OP, Lindsay MP. Epidural opioid analgesia after caesarean section: a comparison of patient-controlled analgesia with meperidine and single bolus injection of morphine. Canadian Journal of Anaesthesia. 1994; 41(11):1063-8

1070. Rosseel PM, van den Broek WG, Boer EC, Prakash O. Epidural sufentanil for intra- and postoperative analgesia in thoracic surgery: a comparative study with intravenous sufentanil. Acta Anaesthesiologica Scandinavica. 1988; 32(3):193-8

1071. Rothwell MP, Pearson D, Hunter JD, Mitchell PA, Graham-Woollard T, Goodwin L et al. Oral oxycodone offers equivalent analgesia to intravenous patient-controlled analgesia after total hip replacement: a randomized, single-centre, non-blinded, non-inferiority study. British Journal of Anaesthesia. 2011; 106(6):865-872

1072. Roussier M, Mahul P, Pascal J, Baylot D, Prades JM, Auboyer C et al. Patient-controlled cervical epidural fentanyl compared with patient-controlled i.v. fentanyl for pain after pharyngolaryngeal surgery. British Journal of Anaesthesia. 2006; 96(4):492-6

1073. Routray SS, Pani N, Mishra D, Nayak S. Comparison of pregabalin with gabapentin as preemptive analgesic in lumbar spine surgery. Journal of Anaesthesiology Clinical Pharmacology. 2018; 34(2):232-236

1074. Rowe NH, Cudmore CL, Turner JL. Control of pain by mefenamic acid following removal of impacted molar. A double-blind, placebo-controlled study. Oral Surgery, Oral Medicine, Oral Pathology. 1981; 51(6):575-80

1075. Roy YM, Derry S, Moore RA. Single dose oral lumiracoxib for postoperative pain in adults. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD006865. DOI: 10.1002/14651858.CD006865.pub2.

1076. Royse C, Royse A, Soeding P, Blake D, Pang J. Prospective randomized trial of high thoracic epidural analgesia for coronary artery bypass surgery. Annals of Thoracic Surgery. 2003; 75(1):93-100

1077. Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A. Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia. Anesthesia and Analgesia. 1993; 77(6):1161-5

1078. Rud O, Konopka C, Schaarschmidt K, Mescha S, Grimm MO, Horstmann M. Influence of the epidural analgesia on postoperative pain in patients after nephrectomy, nephroureterectomy, or nephron-sparing surgery. Journal für Urologie und Urogynäkologie. 2015; 22(4):3-6

1079. Rudra A, Roy S, Roy S, Gupta K, Kundu JP. Postoperative analgesia with extradural buprenorphine and pentazocine. Journal of the Indian Medical Association. 1991; 89(5):123-124

1080. Ruetzler K, Blome CJ, Nabecker S, Makarova N, Fischer H, Rinoesl H et al. A randomised trial of oral versus intravenous opioids for treatment of pain after cardiac surgery. Journal of Anesthesia. 2014; 28(4):580-6

1081. Rundshagen I, Kochs E, Standl T, Schnabel K, Schulte am Esch J. Subarachnoid and intravenous PCA versus bolus administration for postoperative pain relief in orthopaedic patients. Acta Anaesthesiologica Scandinavica. 1998; 42(10):1215-21

1082. Saari TI, Ihmsen H, Mell J, Frohlich K, Fechner J, Schuttler J et al. Influence of intensive care treatment on the protein binding of sufentanil and hydromorphone during pain therapy in postoperative cardiac surgery patients. British Journal of Anaesthesia. 2014; 113(4):677-87

1083. Saarnivaara L, Metsa-Ketela T, Mannisto P, Vapaatalo H. Pain relief and sputum prostaglandins in adults treated with pethidine, tilidine and indomethacin after tonsillectomy. A double-blind study. Acta Anaesthesiologica Scandinavica. 1980; 24(2):79-85

1084. Sacchetti G, Ferrati GC, Parrinello L, Salami A. Kinetics of analgesic response in man; an example with two non-steroidal anti-inflammatory analgesic drugs. Journal of International Medical Research. 1978; 6(4):312-6

1085. Sadove MS, Shulman M, Bomberger C. Comparative study of myfadol and meperidine as postoperative analgesics. Illinois Medical Journal. 1973; 141(3):293-7 passim

1086. Saeed M, Krikor AW, Yaquob ZA, Yihya MW, Khayat HS. Preoperative gabapentin in laparoscopic cholecystectomy. Basrah Journal of Surgery. 2013; 19(1):24-29

1087. Safavi M, Honarmand A, Nematollahy Z. Pre-incisional analgesia with intravenous or subcutaneous infiltration of ketamine reduces postoperative pain in patients after open cholecystectomy: a randomized, double-blind, placebo-controlled study. Pain Medicine. 2011; 12(9):1418-26

1088. Saffer CS, Minkowitz HS, Ding L, Danesi H, Jones JB. Fentanyl iontophoretic transdermal system versus morphine intravenous patient-controlled analgesia for pain management following gynecological surgery: a meta-analysis of randomized, controlled trials. Pain Management. 2015; 5(5):339-48

1089. Sagiroglu G, Copuroglu E, Meydan B, Erturk S, Demir M, Kupeli M. Comparison of epidural or intravenous patient-controlled analgesia at thoracotomy. Gogus Kalp Damar Anestezi ve Yogun Bakim Dernegi Dergisi. 2013; 19(1):10-15

1090. Sagit M, Yalcin S, Polat H, Korkmaz F, Cetinkaya S, Somdas MA. Efficacy of a single preoperative dose of pregabalin for postoperative pain after septoplasty. Journal of Craniofacial Surgery. 2013; 24(2):373-375

1091. Sahin A, Canbay O, Cuhadar A, Celebi N, Aypar U. Bolus ketamine does not decrease hyperalgesia after remifentanil infusion. Pain Clinic. 2004; 16(4):407-411

1092. Said-Ahmed HAF. Dose ranging study of gabapentin for postoperative pain after myomectomy. Acta Anaesthesiologica Italica. 2007; 58(1):23-34

1093. Saito K, Kaneko A, Machii K, Ohta H, Ohkura M, Suzuki M. Efficacy and safety of additional 200-mg dose of celecoxib in adult patients with postoperative pain following extraction of impacted third mandibular molar: a multicenter, randomized, double-blind, placebo-controlled, phase II study in Japan. Clinical Therapeutics. 2012; 34(2):314-28

1094. Sakai T, Use T, Shimamoto H, Fukano T, Sumikawa K. Mini-dose (0.05 mg) intrathecal morphine provides effective analgesia after transurethral resection of the prostate. Canadian Journal of Anaesthesia. 2003; 50(10):1027-30

1095. Salicath J, Yeoh E, Bennett M. Epidural analgesia versus patient-controlled intravenous analgesia for pain following intra-abdominal surgery in adults. Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD010434. DOI: 10.1002/14651858.CD010434.pub2.

1096. Sami Mebazaa M, Mestiri T, Kaabi B, Ben Ammar MS. Clinical benefits related to the combination of ketamine with morphine for patient controlled analgesia after major abdominal surgery. Tunisie Medicale. 2008; 86(5):435-40

1097. Sanders JG, Cameron C, Dawes PJD. Gabapentin in the management of pain following tonsillectomy: A randomized double-blind placebo-controlled trial. Otolaryngology and Head and Neck Surgery. 2017; 157(5):781-790

1098. Sanders JG, Dawes PJD. Gabapentin for perioperative analgesia in otorhinolaryngology-head and neck surgery: Systematic review. Otolaryngology - Head & Neck Surgery. 2016; 155(6):893-903

1099. Sandhu T, Paiboonworachat S, Ko-iam W. Effects of preemptive analgesia in laparoscopic cholecystectomy: a double-blind randomized controlled trial. Surgical Endoscopy. 2011; 25(1):23-7

1100. Sandler AN, Chovaz P, Whiting W. Respiratory depression following epidural morphine: a clinical study. Canadian Anaesthetists' Society Journal. 1986; 33(5):542-9

1101. Sandler AN, Stringer D, Panos L, Badner N, Friedlander M, Koren G et al. A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for postthoracotomy pain relief. Analgesic, pharmacokinetic, and respiratory effects. Anesthesiology. 1992; 77(4):626-34

1102. Sarakatsianou C, Theodorou E, Georgopoulou S, Stamatiou G, Tzovaras G. Effect of pre-emptive pregabalin on pain intensity and postoperative morphine consumption after laparoscopic cholecystectomy. Surgical Endoscopy. 2013; 27(7):2504-11

1103. Sarmiento-Ramirez NL, Hernandez-Jimenez A. Clinical experience of mixed blockade with continuous postoperative analgesia and epidural blockade with intravenous postoperative analgesia in caesarean section. Revista Mexicana de Anestesiologia. 2007; 30(4):216-219

1104. Sarridou DG, Chalmouki G, Braoudaki M, Koutsoupaki A, Mela A, Vadalouka A. Intravenous parecoxib and continuous femoral block for postoperative analgesia after total knee arthroplasty. A randomized, double-blind, prospective trial. Pain Physician. 2015; 18(3):267-76

1105. Sarvela J, Halonen P, Soikkeli A, Korttila K. A double-blinded, randomized comparison of intrathecal and epidural morphine for elective cesarean delivery. Anesthesia and Analgesia. 2002; 95(2):436-40

1106. Satomi S, Kakuta N, Murakami C, Sakai Y, Tanaka K, Tsutsumi YM. The efficacy of programmed intermittent epidural bolus for postoperative analgesia after open gynecological surgery: A randomized double-blinded study. BioMed Research International. 2018; 2018:6297247

1107. Sava M, Rusu N. Effects of gabapentin on preoperative anxiety and postoperative analgesia with morphine in rectocolic surgery. Romanian Journal of Anaesthesia and Intensive Care. 2009; 16:10-16

1108. Sawaddiruk P, Paiboonworachat S, Janthawichai K. Comparison of efficacy and effectiveness between ULTRACET and tramadol/acetaminophen in acute postoperative pain after upper extremity surgery. Journal of the Medical Association of Thailand. 2010; 93(7):812-817

1109. Sawchuk CW, Ong B, Unruh HW, Horan TA, Greengrass R. Thoracic versus lumbar epidural fentanyl for postthoracotomy pain. Annals of Thoracic Surgery. 1993; 55(6):1472-6

1110. Scarfe AJ, Schuhmann-Hingel S, Duncan JK, Ma N, Atukorale YN, Cameron AL. Continuous paravertebral block for post-cardiothoracic surgery analgesia: a systematic review and meta-analysis. European Journal of Cardio-Thoracic Surgery. 2016; 50(6):1010-1018

1111. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999; 82(2):111-25

1112. Schnabel A, Reichl SU, Kranke P, Pogatzki-Zahn EM, Zahn PK. Efficacy and safety of paravertebral blocks in breast surgery: a meta-analysis of randomized controlled trials. British Journal of Anaesthesia. 2010; 105(6):842-52

1113. Scholz A, Bothmer J, Kok M, Hoschen K, Daniels S. Cebranopadol: A novel, first-in-class, strong analgesic: Results from a randomized phase IIa clinical trial in postoperative acute pain. Pain Physician. 2018; 21(3):E193-E206

1114. Schraag S, Checketts MR, Kenny GNC. Lack of rapid development of opioid tolerance during alfentanil and remifentanil infusions for postoperative pain. Anesthesia and Analgesia. 1999; 89(3):753-757

1115. Schulze S, Roikjaer O, Hasselstrom L, Jensen NH, Kehlet H. Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain but not systemic response and convalescence after cholecystectomy. Surgery. 1988; 103(3):321-7

1116. Schumann R, Shikora S, Weiss JM, Wurm H, Strassels S, Carr DB. A comparison of multimodal perioperative analgesia to epidural pain management after gastric bypass surgery. Anesthesia and Analgesia. 2003; 96(2):469-74

1117. Scott NB, James K, Murphy M, Kehlet H. Continuous thoracic epidural analgesia versus combined spinal/thoracic epidural analgesia on pain, pulmonary function and the metabolic response following colonic resection. Acta Anaesthesiologica Scandinavica. 1996; 40(6):691-6

1118. Scott R, Ellis E, 3rd, Upton LG. Double-blind evaluation of etodolac (200 mg, 400 mg) compared with zomepirac (100 mg) and placebo on third molar extraction pain. Oral Surgery, Oral Medicine, Oral Pathology. 1986; 62(6):638-42

1119. Secrist ES, Freedman KB, Ciccotti MG, Mazur DW, Hammoud S. Pain management after outpatient anterior cruciate ligament reconstruction: a systematic review of randomized controlled trials. American Journal of Sports Medicine. 2016; 44(9):2435-47

1120. Sehgal R, Agarwal N, Khatuja A, Krishna HM, Bhadoria P, Kumar R. Comparative efficacy of ketoprofen and diclofenac sodium for post operative pain relief. Journal of Anaesthesiology Clinical Pharmacology. 2003; 19(3):307-311

1121. Sekhavat L, Zare F, Mojibian M. The postoperative analgesic effects of low-dose gabapentin in patients undergoing abdominal hysterectomy. South African Journal of Obstetrics and Gynaecology. 2009; 15(1):37-40

1122. Sekiguchi H, Inoue G, Nakazawa T, Imura T, Saito W, Uchida K et al. Loxoprofen sodium and celecoxib for postoperative pain in patients after spinal surgery: a randomized comparative study. Journal of Orthopaedic Science. 2015; 20(4):617-23

1123. Sen H, Sizlan A, Yanarates O, Inangil G, Ozkan S, Dagli G. The effects of gabapentin on acute and chronic pain after inguinal herniorraphy. Pain Practice. 2009; 9(S1):151

1124. Sen S, Ozmert G, Aydin ON, Baran N, Caliskan E. The persisting analgesic effect of low-dose intravenous ketamine after spinal anaesthesia for caesarean section. European Journal of Anaesthesiology. 2005; 22(7):518-23

1125. Senagore AJ, Delaney CP, Mekhail N, Dugan A, Fazio VW. Randomized clinical trial comparing epidural anaesthesia and patient-controlled analgesia after laparoscopic segmental colectomy. British Journal of Surgery. 2003; 90(10):1195-9

1126. Senard M, Deflandre EP, Ledoux D, Roediger L, Hubert BM, Radermecker M et al. Effect of celecoxib combined with thoracic epidural analgesia on pain after thoracotomy. British Journal of Anaesthesia. 2010; 105(2):196-200

1127. Sener M, Ozgur Pektas Z, Yilmaz I, Turkoz A, Uckan S, Donmez A et al. Comparison of preemptive analgesic effects of a single dose of nonopioid analgesics for pain management after ambulatory surgery: a prospective, randomized, single-blind studyin Turkish patients. Current Therapeutic Research - Clinical and Experimental. 2005; 66(6):541-551

1128. Sener M, Yilmazer C, Yilmaz I, Bozdogan N, Ozer C, Donmez A et al. Efficacy of lornoxicam for acute postoperative pain relief after septoplasty: a comparison with diclofenac, ketoprofen, and dipyrone. Journal of Clinical Anesthesia. 2008; 20(2):103-8

1129. Senturk M, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalcin S et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesthesia and Analgesia. 2002; 94(1):11-5

1130. Seo DK, Lee CJ, Kim JS. A comparison of oxycodone and fentanyl in the management of early postoperative pain and for patient-controlled analgesia after total abdominal hysterectomy. Anesthesiology and Pain Medicine. 2016; 11(2):176-181

1131. Seymour RA. Analgesic efficacy and plasma concentration of three analgesics in pain after lower third molar removal. SAAD Digest. 1983; 5(7):172-88

1132. Seymour RA, Watkinson H, Hawkesford JE, Moore U. The efficacy of buffered ketoprofen in postoperative pain after third molar surgery. European Journal of Clinical Pharmacology. 2000; 55(11-12):801-6

1133. Shaffer EE, Pham A, Woldman RL, Spiegelman A, Strassels SA, Wan GJ et al. Estimating the effect of intravenous acetaminophen for postoperative pain management on length of stay and inpatient hospital costs. Advances in Therapy. 2017; 33(12):2211-2228

1134. Shah VR, Rawal R, Marda M. Pre-emptive effect of epidural buprenorphine with ketamine on postoperative pain after lower urinary tract surgery. Indian Journal of Anaesthesia. 2006; 50(4):271-274

1135. Shahbazi S, Talei A, Besharati A, Shamsnia SJ. Comparison of serum cortisol level in open heart surgery--morphine versus sufentanil. Middle East Journal of Anesthesiology. 2004; 17(5):969-74

1136. Shao CJ, Xu BQ, Zhou DC. Comparison of postoperative analgesia between different protocols of epidural morphine in abdominal hysterectomy. Chinese Pharmacological Bulletin. 2010; 26(12):1595-1597

1137. Sharar SR, Ready LB, Ross BK, Chadwick HS, Sudy DJ. A comparison of postcesarean epidural morphine analgesia by single injection and by continuous infusion. Regional Anesthesia. 1991; 16(4):232-5

1138. Shi WZ, Miao YL, Yakoob MY, Cao JB, Zhang H, Jiang YG et al. Recovery of gastrointestinal function with thoracic epidural vs. systemic analgesia following gastrointestinal surgery. Acta Anaesthesiologica Scandinavica. 2014; 58(8):923-32

1139. Shulman M, Sandler AN, Bradley JW. Posthoracotomy pain and pulmonary function following epidural and systemic morphine Anesthesiology. 1984; 61(5):569-575

1140. Siddiqui AK, Sadat-Ali M, Al-Ghamdi AA, Mowafi HA, Ismail SA, Al-Dakheel DA. The effect of etoricoxib premedication on postoperative analgesia requirement in orthopedic and trauma patients. Saudi Medical Journal. 2008; 29(7):966-70

1141. Siddiqui NT, Fischer H, Guerina L, Friedman Z. Effect of a preoperative gabapentin on postoperative analgesia in patients with inflammatory bowel disease following major bowel surgery: a randomized, placebo-controlled trial. Pain Practice. 2014; 14(2):132-9

1142. Sidebotham DA, Reddy M, Schug SA. Influence of postoperative pain therapy on nausea and vomiting. Schmerz. 1997; 11(4):241-246

1143. Sidiropoulou T, Giavasopoulos E, Kostopanagiotou G, Vafeiadou M, Lioulias A, Stamatakis E et al. Perioperative pregabalin for postoperative pain relief after thoracotomy. Journal of Anesthesia and Surgery. 2016; 3(1):0-0

1144. Sierra F, Ortiz J, Rodríguez R, García A. Control of postoperative acute pain with opioids administered by epidural catheter in non-specialized units for the treatment of pain. Medicina Militar. 1995; 51(2):161-165

1145. Silva de Oliveira JC, Grossi de Oliveira GA, Bassi AP. Comparative assessment of the effect of ibuprofen and etodolac on edema, trismus, and pain in lower third molar surgery: A randomized clinical trial. Journal of Oral and Maxillofacial Surgery. 2016; 74(8):1524-30

1146. Silva EP, Sakata RK, Garcia JB, Salomao R, Issy AM. Evaluation of preemptive effect of epidural S(+)-ketamine for hysterectomy: plasmatic concentrations of interleukins. Revista Brasileira de Anestesiologia. 2012; 62(1):3-9

1147. Silvanto M, Lappi M, Rosenberg PH. Comparison of the opioid-sparing efficacy of diclofenac and ketoprofen for 3 days after knee arthroplasty. Acta Anaesthesiologica Scandinavica. 2002; 46(3):322-8

1148. Silvasti M, Pitkanen M. Continuous epidural analgesia with bupivacaine-fentanyl versus patient-controlled analgesia with i.v. morphine for postoperative pain relief after knee ligament surgery. Acta Anaesthesiologica Scandinavica. 2000; 44(1):37-42

1149. Silvasti M, Pitkanen M. Patient-controlled epidural analgesia versus continuous epidural analgesia after total knee arthroplasty. Acta Anaesthesiologica Scandinavica. 2001; 45(4):471-6

1150. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology. 2005; 102(4):822-31

1151. Sinatra RS, Sevarino FB, Chung JH, Graf G, Paige D, Takla V et al. Comparison of epidurally administered sufentanil, morphine, and sufentanil-morphine combination for postoperative analgesia. Anesthesia and Analgesia. 1991; 72(4):522-7

1152. Sindhvananda W, Leelanukrom R, Rodanant O, Sriprajittichai P. Maternal satisfaction to epidural and spinal anesthesia for cesarean section. Journal of the Medical Association of Thailand. 2004; 87(6):628-635

1153. Singelyn FJ, Deyaert M, Joris D, Pendeville E, Gouverneur JM. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. Anesthesia and Analgesia. 1998; 87(1):88-92

1154. Singelyn FJ, Ferrant T, Malisse MF, Joris D. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous femoral nerve sheath block on rehabilitation after unilateral total-hip arthroplasty. Regional Anesthesia and Pain Medicine. 2005; 30(5):452-7

1155. Singelyn FJ, Gouverneur JMA. Postoperative analgesia after total hip arthroplasty: i.v. PCA with morphine, patient-controlled epidural analgesia, or continuous '3-in-1' block?: a prospective evaluation by our acute pain service in more than 1,300 patients. Journal of Clinical Anesthesia. 1999; 11(7):550-554

1156. Singh AP, Kaur R, Gupta R, Kumari A. Intrathecal buprenorphine versus fentanyl as adjuvant to 0.75% ropivacaine in lower limb surgeries. Journal of Anaesthesiology Clinical Pharmacology. 2016; 32(2):229-233

1157. Singh H, Kundra S, Singh RM, Grewal A, Kaul TK, Sood D. Preemptive analgesia with ketamine for laparoscopic cholecystectomy. Journal of Anaesthesiology Clinical Pharmacology. 2013; 29(4):478-84

1158. Singh RK, Saini AM, Goel N, Bisht D, Seth A. Major laparoscopic surgery under regional anesthesia: a prospective feasibility study. Armed Forces Medical Journal, India. 2015; 71(2):126-131

1159. Singh V, Singh VP, Shankar RR. Post operative pain relief in caesarean section. Medical Journal Armed Forces India. 2001; 57(1):31-4

1160. Singh YA, Singh TH, Siram A, Fimlalkim O, Eshori L, Thokchom RS. A comparative study of epidural tramadol hydrochloride and epidural buprenorphine hydrochloride for postoperative analgesia following combined spinal epidural anaesthesia. Journal of Medical Society. 2009; 23(2):83-87

1161. Singhal AK, Mishra S, Bhatnagar S, Singh R. Epidural morphine analgesia compared with intravenous morphine for oral cancer surgery with pectoralis major myocutaneous flap reconstruction. Acta Anaesthesiologica Scandinavica. 2006; 50(2):234-8

1162. Singla N, Barrett T, Sisk L, Kostenbader K, Young J. Assessment of the safety and efficacy of extended-release oxycodone/acetaminophen, for 14 days postsurgery. Current Medical Research and Opinion. 2014; 30(12):2571-8

1163. Singla N, Barrett T, Sisk L, Kostenbader K, Young J, Giuliani M. A randomized, double-blind, placebo-controlled study of the efficacy and safety of MNK-795, a dual-layer, biphasic, immediate-release and extended-release combination analgesic for acute pain. Current Medical Research and Opinion. 2014; 30(3):349-359

1164. Singla N, Minkowitz HS, Soergel DG, Burt DA, Subach RA, Salamea MY et al. A randomized, Phase IIb study investigating oliceridine (TRV130), a novel micro - receptor G-protein pathway selective (mu-GPS) modulator, for the management of moderate to severe acute pain following abdominoplasty. Journal of Pain Research. 2017; 10:2413-2424

1165. Siribumrungwong K, Cheewakidakarn J, Tangtrakulwanich B, Nimmaanrat S. Comparing parecoxib and ketorolac as preemptive analgesia in patients undergoing posterior lumbar spinal fusion: a prospective randomized double-blinded placebo-controlled trial. BMC Musculoskeletal Disorders. 2015; 16:59

1166. Skoglund LA. A new paracetamol/paracetamol-methionine ester combination effects on postoperative course. European Journal of Clinical Pharmacology. 1986; 31(1):45-8

1167. Skoglund LA, Skjelbred P. Comparison of a traditional paracetamol medication and a new paracetamol/paracetamol-methionine ester combination. European Journal of Clinical Pharmacology. 1984; 26(5):573-7

1168. Skoglund LA, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen 1000 mg, acetaminophen 2000 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg versus placebo in acute postoperative pain. Pharmacotherapy. 1991; 11(5):364-9

1169. Slinger P, Shennib H, Wilson S. Postthoracotomy pulmonary function: a comparison of epidural versus intravenous meperidine infusions. Journal of Cardiothoracic and Vascular Anesthesia. 1995; 9(2):128-34

1170. Sloan PA, Barkin RL. Oxymorphone and oxymorphone extended release: a pharmacotherapeutic review. Journal of Opioid Management. 2008; 4(3):131-144

1171. Smirnov G, Terava M, Tuomilehto H, Hujala K, Seppanen M, Kokki H. Etoricoxib for pain management during thyroid surgery--a prospective, placebo-controlled study. Otolaryngology - Head & Neck Surgery. 2008; 138(1):92-7

1172. Smith AB, Ravikumar TS, Kamin M, Jordan D, Xiang J, Rosenthal N et al. Combination tramadol plus acetaminophen for postsurgical pain. American Journal of Surgery. 2004; 187(4):521-7

1173. Smith CV, Rayburn WF, Karaiskakis PT, Morton RD, Norvell MJ. Comparison of patient-controlled analgesia and epidural morphine for postcesarean pain and recovery. Journal of Reproductive Medicine. 1991; 36(6):430-434

1174. Smith LA, Moore RA, McQuay HJ, Gavaghan D. Using evidence from different sources: an example using paracetamol 1000 mg plus codeine 60 mg. BMC Medical Research Methodology. 2001; 1:1

1175. Sng BL, Kwok SC, Mathur D, Ithnin F, Newton-Dunn C, Assam PN et al. Comparison of epidural oxycodone and epidural morphine for post-caesarean section analgesia: A randomised controlled trial. Indian Journal of Anaesthesia. 2016; 60(3):187-93

1176. Snijdelaar DG, Cornelisse HB, Schmid RL, Katz J. A randomised, controlled study of peri-operative low dose s(+)-ketamine in combination with postoperative patient-controlled s(+)-ketamine and morphine after radical prostatectomy. Anaesthesia. 2004; 59(3):222-8

1177. Solak O, Metin M, Esme H, Solak O, Yaman M, Pekcolaklar A et al. Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain. European Journal of Cardio-Thoracic Surgery. 2007; 32(1):9-12

1178. Soltanzadeh M, Ebad A, Pipelzadeh M, Tabatabaei S, Dehghani Firouzabadi M, Vasigh A et al. Gabapentin may relieve post-coronary artery bypass graft pain: A double blind randomized clinical trial. Iranian Cardovascular Research Journal. 2011; 5(3):e13826

1179. Somri M, Hawash N, Hadjittofi C, Ghantous-Toukan M, Tome R, Yodashkin M et al. Protective multimodal analgesia with etoricoxib and spinal anesthesia in inguinal hernia repair: a randomized controlled trial. Journal of Anesthesia. 2017; 31(5):645-650

1180. Song JW, Shim JK, Song Y, Yang SY, Park SJ, Kwak YL. Effect of ketamine as an adjunct to intravenous patient-controlled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery. British Journal of Anaesthesia. 2013; 111(4):630-5

1181. Song YK, Lee C, Seo DH, Park SN, Moon SY, Park CH. Interaction between postoperative shivering and hyperalgesia caused by high-dose remifentanil. Korean Journal of Anesthesiology. 2014; 66(1):44-51

1182. Souzdalnitski D, Rech GR, Naydinskiy A, Suzdalnitskaya D, Isakov RV, Guirguis M. Ketamine in perioperative analgesia for knee surgeries: Review of evidence from randomized controlled trials. Techniques in Regional Anesthesia and Pain Management. 2014; 18(4):130-136

1183. Spence AA, Smith G, Harris R. The influence of post-operative analgesia and operative procedure on post-operative lung function: a comparison of morphine with extradural nerve block. Anaesthesia. 1970; 25(1):126

1184. Spence D, Goff J, Mohan E, Bowen K, Osborne L, Maye J. Perioperative administration of gabapentin for shoulder arthroscopy: a prospective, randomized, double-blind, placebo-controlled study. AANA Journal. 2011; 79(4 Suppl):S43-50

1185. Spreng UJ, Dahl V, Raeder J. Effects of perioperative S (+) ketamine infusion added to multimodal analgesia in patients undergoing ambulatory haemorrhoidectomy. Scandinavian Journal of Pain. 2010; 1(2):100-105

1186. Spreng UJ, Dahl V, Raeder J. Effect of a single dose of pregabalin on post-operative pain and pre-operative anxiety in patients undergoing discectomy. Acta Anaesthesiologica Scandinavica. 2011; 55(5):571-6

1187. Srivastava S, Gupta D, Naz A, Rizvi MM, Singh PK. Effects of preoperative single dose Etoricoxib on postoperative pain and sleep after lumbar diskectomy: prospective randomized double blind controlled study. Middle East Journal of Anesthesiology. 2012; 21(5):725-30

1188. Srivastava U, Kumar A, Saxena S, Mishra AR, Saraswat N, Mishra S. Effect of preoperative gabapentin on postoperative pain and tramadol consumption after minilap open cholecystectomy: a randomized double-blind, placebo-controlled trial. European Journal of Anaesthesiology. 2010; 27(4):331-5

1189. St. Peter SD, Weesner KA, Weissend EE, Sharp SW, Valusek PA, Sharp RJ et al. Epidural vs patient-controlled analgesia for postoperative pain after pectus excavatum repair: a prospective, randomized trial. Journal of Pediatric Surgery. 2012; 47(1):148-153

1190. Stamenkovic DM, Geric V, Slavkovic Z, Raskovic J, Djordjevic M. Combined spinal-epidural analgesia vs. intermittent bolus epidural analgesia for pain relief after major abdominal surgery. A prospective, randomised, double-blind clinical trial. International Journal of Clinical Practice. 2008; 62(2):255-62

1191. Staren ED, Cullen ML. Epidural catheter analgesia for the management of postoperative pain. Surgery, Gynecology and Obstetrics. 1986; 162(4):389-404

1192. Steagall PV, Benito J, Monteiro BP, Doodnaught GM, Beauchamp G, Evangelista MC. Analgesic effects of gabapentin and buprenorphine in cats undergoing ovariohysterectomy using two pain-scoring systems: a randomized clinical trial. Journal of Feline Medicine and Surgery. 2018; 20(8):741-748

1193. Stegmann JU, Weber H, Steup A, Okamoto A, Upmalis D, Daniels S. The efficacy and tolerability of multiple-dose tapentadol immediate release for the relief of acute

pain following orthopedic (bunionectomy) surgery. Current Medical Research and Opinion. 2008; 24(11):3185-96

1194. Stehling LC, Zauder HL. Double-blind comparison of butorphanol and meperidine in the treatment of post-surgical pain. Journal of International Medical Research. 1978; 6(4):306-311

1195. Steinberg AC, Schimpf MO, White AB, Mathews C, Ellington DR, Jeppson P et al. Preemptive analgesia for postoperative hysterectomy pain control: systematic review and clinical practice guidelines. American Journal of Obstetrics and Gynecology. 2017; 217(3):303-313.e6

1196. Steinberg RB, Liu SS, Wu CL, Mackey DC, Grass JA, Ahlen K et al. Comparison of ropivacaine-fentanyl patient-controlled epidural analgesia with morphine intravenous patient-controlled analgesia for perioperative analgesia and recovery after open colon surgery. Journal of Clinical Anesthesia. 2002; 14(8):571-577

1197. Stenseth R, Bjella L, Berg EM, Christensen O, Levang OW, Gisvold SE. Effects of thoracic epidural analgesia on pulmonary function after coronary artery bypass surgery. European Journal of Cardio-Thoracic Surgery. 1996; 10(10):859-65; discussion 866

1198. Stevens RA, Urmey WF, Urquhart BL, Kao TC. Back pain after epidural anesthesia with chloroprocaine. Anesthesiology. 1993; 78(3):492-7

1199. Stoddart PA, Cooper A, Russell R, Reynolds F. A comparison of epidural diamorphine with intravenous patient-controlled analgesia using the Baxter infusor following caesarean section. Anaesthesia. 1993; 48(12):1086-90

1200. Stoelting VK. Analgesic action of pentazocine compared with morphine in postoperative pain. Anesthesia and Analgesia. 1965; 44(6):769-72

1201. Stott A. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. Nursing Standard. 2017; 31(48):42-43

1202. Striebel HW, Scheitza W, Philippi W, Behrens U, Toussaint S. Quantifying oral analgesic consumption using a novel method and comparison with patient-controlled intravenous analgesic consumption. Anesthesia and Analgesia. 1998; 86(5):1051-3

1203. Striebel HW, Wilker E. The management of postoperative pain following total hip replacement with a continuous 3-in-1 block. Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie. 1993; 28(3):168-173

1204. Stuardo C, Lobos-Urbina D, Altermatt F. Is intravenous ketamine effective for postoperative pain management in adults? Medwave. 2017; 17(Suppl2):e6952

1205. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiologica Scandinavica. 1997; 41(9):1124-32

1206. Subramaniam B, Subramaniam K, Pawar DK, Sennaraj B. Preoperative epidural ketamine in combination with morphine does not have a clinically relevant intra- and postoperative opioid-sparing effect. Anesthesia and Analgesia. 2001; 93(5):1321-6

1207. Subramaniam K, Akhouri V, Glazer PA, Rachlin J, Kunze L, Cronin M et al. Intra- and postoperative very low dose intravenous ketamine infusion does not increase pain relief after major spine surgery in patients with preoperative narcotic analgesic intake. Pain Medicine. 2011; 12(8):1276-83

1208. Subramaniam K, Subramaniam B, Pawar DK, Kumar L. Evaluation of the safety and efficacy of epidural ketamine combined with morphine for postoperative analgesia after major upper abdominal surgery. Journal of Clinical Anesthesia. 2001; 13(5):339-344

1209. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesthesia and Analgesia. 2004; 99(2):482-95

1210. Sultan A, McQuay HJ, Moore RA, Derry S. Single dose oral flurbiprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD007358. DOI: 10.1002/14651858.CD007358.pub2.

1211. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B. The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: A meta-analysis. Anesthesia and Analgesia. 2016; 123(1):154-64

1212. Sumida S, Lesley MR, Hanna MN, Murphy JD, Kumar K, Wu CL. Meta-analysis of the effect of extended-release epidural morphine versus intravenous patient-controlled analgesia on respiratory depression. Journal of Opioid Management. 2009; 5(5):301-305

1213. Sun L, Zhu X, Zou J, Li Y, Han W. Comparison of intravenous and oral acetaminophen for pain control after total knee and hip arthroplasty: A systematic review and meta-analysis. Medicine. 2018; 97(6):e9751

1214. Sun Y, Liu Y. Efficacy of preemptive gabapentin for laparoscopic cholecystectomy: A meta-analysis of randomized controlled trials. International Journal of Clinical and Experimental Medicine. 2016; 9(8):15157-15166

1215. Sundar AS, Kodali R, Sulaiman S, Ravullapalli H, Karthekeyan R, Vakamudi M. The effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting. Annals of Cardiac Anaesthesia. 2012; 15(1):18-25

1216. Sunshine A, Olson NZ, Colon A, Rivera J, Kaiko RF, Fitzmartin RD et al. Analgesic efficacy of controlled-release oxycodone in postoperative pain. Journal of Clinical Pharmacology. 1996; 36(7):595-603

1217. Sunshine A, Olson NZ, Zighelboim I, DeCastro A, Minn FL. Analgesic oral efficacy of tramadol hydrochloride in postoperative pain. Clinical Pharmacology and Therapeutics. 1992; 51(6):740-6

1218. Suppa E, Valente A, Catarci S, Zanfini BA, Draisci G. A study of low-dose S-ketamine infusion as "preventive" pain treatment for cesarean section with spinal anesthesia: benefits and side effects. Minerva Anestesiologica. 2012; 78(7):774-81

1219. Sutters KA. "A randomized clinical trial of the efficacy of scheduled dosing of acetaminophen and hydrocodone for the management of postoperative pain in children after tonsillectomy": reply. Clinical Journal of Pain. 2011; 27(1):90-91

1220. Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimada Y, Sakamoto A. Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. Anesthesiology. 2006; 105(1):111-9

1221. Suzuki M, Tsueda K, Lansing PS, Tolan MM, Fuhrman TM, Ignacio CI et al. Small-dose ketamine enhances morphine-induced analgesia after outpatient surgery. Anesthesia and Analgesia. 1999; 89(1):98-103

1222. Sveticic G, Farzanegan F, Zmoos P, Zmoos S, Eichenberger U, Curatolo M. Is the combination of morphine with ketamine better than morphine alone for postoperative intravenous patient-controlled analgesia? Anesthesia and Analgesia. 2008; 106(1):287-93

1223. Sviggum HP, Arendt KW, Jacob AK, Niesen AD, Johnson RL, Schroeder DR et al. Intrathecal hydromorphone and morphine for postcesarean delivery analgesia: Determination of the ED90 using a sequential allocation biased-coin method. Anesthesia and Analgesia. 2016; 123(3):690-7

1224. Swaroop NS, Batra YK, Bhardwaj N, Chari P, Ram P. A comparative evaluation of thoracic and lumbar epidural fentanyl for post thoracotomy pain. Annals of Cardiac Anaesthesia. 2002; 5(1):53-8

1225. Swenson JD, Hullander RM, Bready RJ, Leivers D. A comparison of patient controlled epidural analgesia with sufentanil by the lumbar versus thoracic route after thoracotomy. Anesthesia and Analgesia. 1994; 78(2):215-218

1226. Swerdlow M, Starmer G, Daw RH. A comparison of morphine and phenazocine in postoperative pain. British Journal of Anaesthesia. 1964; 36:782-786

1227. Syal K, Goma M, Dogra RK, Ohri A, Gupta AK, Goel A. "Protective premedication": a comparative study of acetaminophen, gabapentin and combination of acetaminophen with gabapentin for post-operative analgesia. Journal of Anaesthesiology, Clinical Pharmacology. 2010; 26(4):531-6

1228. Tai YM, Baker R. Comparison of controlled-release ketoprofen and diclofenac in the control of post-surgical dental pain. Journal of the Royal Society of Medicine. 1992; 85(1):16-8

1229. Takahashi W, Okazaki J, Yamamoto T, Nishino T. Effects of simultaneous epidural administration of ropivacaine and morphine on the post-operative pain in the gynecologic patients. Japanese Journal of Anesthesiology. 2005; 54(2):126-132

1230. Takenaka-Hamaya C, Hamaya Y, Dohi S. Epidural morphine injection after combined spinal and epidural anaesthesia. European Journal of Anaesthesiology. 2002; 19(9):672-6

1231. Takmaz SA, Kaymak C, Pehlivan BS, Dikmen B. [Effect of preoperative 900 and 1200 mg single oral dose of gabapentin on postoperative pain relief and tramadol consumption in open cholecystectomy surgery]. Agri. 2007; 19(3):32-8

1232. Tammisto T, Takki S. A comparison of pentazocine and pethidine in patients with pain following cholecystectomy. British Journal of Anaesthesia. 1971; 43(1):58-64

1233. Tan CH, Wong WSH, Onsiong MK, Chan MK, Chiu KYW, Tai CM. A baseline audit of the efficacy and safety of an acute pain service (APS) for cesarean section patients. Acute Pain. 2003; 4(3-4):99-104

1234. Tan PH, Chia YY, Perng JS, Chou AK, Chung HC, Lee CC. Intermittent bolus versus patient-controlled epidural morphine for postoperative analgesia. Acta Anaesthesiologica Sinica. 1997; 35(3):149-54

1235. Tan PH, Kuo MC, Kao PF, Chia YY, Liu K. Patient-controlled epidural analgesia with morphine or morphine plus ketamine for post-operative pain relief. European Journal of Anaesthesiology. 1999; 16(12):820-5

1236. Tan TL, Longenecker AS, Rhee JH, Good RP, Emper WD, Freedman KB et al. Intraoperative ketamine in total knee arthroplasty does not decrease pain and

narcotic consumption: A prospective randomized controlled trial. Journal of Arthroplasty. 2019; 34(8):1640-1645

1237. Tanaka M, Watanabe S, Ashimura H, Akiyoshi Y, Nishijima Y, Sato S et al. Minimum effective combination dose of epidural morphine and fentanyl for posthysterectomy analgesia: a randomized, prospective, double-blind study. Anesthesia and Analgesia. 1993; 77(5):942-6

1238. Tanaka M, Watanabe S, Endo T, Okane M, Hamaya Y. Combination of epidural morphine and fentanyl for postoperative analgesia. Regional Anesthesia. 1991; 16(4):214-7

1239. Tang J, Li S, White PF, Chen X, Wender RH, Quon R et al. Effect of parecoxib, a novel intravenous cyclooxygenase type-2 inhibitor, on the postoperative opioid requirement and quality of pain control. Anesthesiology. 2002; 96(6):1305-9

1240. Tang YY, Lin XM, Huang W, Jiang XQ. Addition of low-dose ketamine to propofol-fentanyl sedation for gynecologic diagnostic laparoscopy: randomized controlled trial. Journal of Minimally Invasive Gynecology. 2010; 17(3):325-30

1241. Tanskanen P, Kytta J, Randell T. Patient-controlled analgesia with oxycodone in the treatment of postcraniotomy pain. Acta Anaesthesiologica Scandinavica. 1999; 43(1):42-5

1242. Taqi A, Hong X, Mistraletti G, Stein B, Charlebois P, Carli F. Thoracic epidural analgesia facilitates the restoration of bowel function and dietary intake in patients undergoing laparoscopic colon resection using a traditional, nonaccelerated, perioperative care program. Surgical Endoscopy. 2007; 21(2):247-52

1243. Tarkkila P, Saarnivaara L. Ketoprofen, diclofenac or ketorolac for pain after tonsillectomy in adults? British Journal of Anaesthesia. 1999; 82(1):56-60

1244. Tarkkila P, Tuominen M, Rosenberg PH. Intravenous ketorolac vs diclofenac for analgesia after maxillofacial surgery. Canadian Journal of Anaesthesia. 1996; 43(3):216-20

1245. Tarradell R, Pol O, Farre M, Barrera E, Puig MM. Respiratory and analgesic effects of meperidine and tramadol in patients undergoing orthopedic surgery. Methods and Findings in Experimental and Clinical Pharmacology. 1996; 18(3):211-8

1246. Taura P, Fuster J, Blasi A, Martinez-Ocon J, Anglada T, Beltran J et al. Postoperative pain relief after hepatic resection in cirrhotic patients: the efficacy of a single small dose of ketamine plus morphine epidurally. Anesthesia and Analgesia. 2003; 96(2):475-80

1247. Taverne RH, Ionescu TI, Nuyten ST. Comparative absorption and distribution pharmacokinetics of intravenous and epidural sufentanil for major abdominal surgery. Clinical Pharmacokinetics. 1992; 23(3):231-7

1248. Tayyem M, Elhadid F, Haddad R, Samarah O, Ananzah M, Ahmad M et al. Perioperative use of pregabalin in total knee arthroplasty: Meta-analysis of randomized controlled trials. Journal of Musculoskeletal Research. 2017; 20(2):1750009

1249. Tegon G, Pulzato L, Passarella L, Guidolin D, Zusso M, Giusti P. Randomized placebo-controlled trial on local applications of opioids after hemorrhoidectomy. Techniques in Coloproctology. 2009; 13(3):219-24

1250. Tena B, Gomar C, Rios J. Perioperative epidural or intravenous ketamine does not improve the effectiveness of thoracic epidural analgesia for acute and chronic pain after thoracotomy. Clinical Journal of Pain. 2014; 30(6):490-500

1251. Tenenbein PK, Debrouwere R, Maguire D, Duke PC, Muirhead B, Enns J et al. Thoracic epidural analgesia improves pulmonary function in patients undergoing cardiac surgery. Canadian Journal of Anaesthesia. 2008; 55(6):344-50

1252. Tenopala Villegas S, Hernandez Santos JR, Rivera Leon G. Control of postoperatory pelvic pain with continuous epidural meperidine infusion with a pressure paragon pump. Revista Mexicana de Anestesiologia. 1999; 22(4):234-237

1253. Terracina S, Robba C, Prete A, Sergi PG, Bilotta F. Prevention and treatment of postoperative pain after lumbar spine procedures: A systematic review. Pain Practice. 2018; 18(7):925-945

1254. Thomson CA, Becker DR, Messick JM, Jr., de Castro MA, Pairolero PC, Trastek VF et al. Analgesia after thoracotomy: effects of epidural fentanyl concentration/infusion rate. Anesthesia and Analgesia. 1995; 81(5):973-81

1255. Thongrong P, Jarruwale P, Panichkul P. Effectiveness of paracervical block versus intravenous morphine during uterine curettage: a randomized controlled trial. Journal of the Medical Association of Thailand. 2011; 94(4):403-407

1256. Tigerstedt I, Turunen M, Tammisto T, Hastbacka J. The effect of buprenorphine and oxycodone on the intracholedochal passage pressure. Acta Anaesthesiologica Scandinavica. 1981; 25(2):99-102

1257. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesthesia and Analgesia. 2007; 104(6):1545-56

1258. Tirunagari SK, Derry S, Moore RA, McQuay HJ. Single dose oral etodolac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD007357. DOI: 10.1002/14651858.CD007357.pub2.

1259. Titsworth WL, Abram J, Guin P, Herman MA, West J, Davis NW et al. A prospective time-series quality improvement trial of a standardized analgesia protocol to reduce postoperative pain among neurosurgery patients. Journal of Neurosurgery. 2016; 125(6):1523-1532

1260. Tiwari AK, Tayal S, Chadha M, Ganguly S, Mandhyan R. Effect of oral clonidine, etoricoxib, and gabapentin as premedication on sensory and motor blocks and post operative analgesia in surgeries under subarachnoid block using bupivacaine. American Journal of Therapeutics. 2014; 21(3):143-7

1261. Toivonen J, Pitko VM, Rosenberg PH. Etoricoxib pre-medication combined with intra-operative subacromial block for pain after arthroscopic acromioplasty. Acta Anaesthesiologica Scandinavica. 2007; 51(3):316-21

1262. Toms L, Derry S, Moore R, McQuay H. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001547. DOI: 10.1002/14651858.CD001547.pub2.

1263. Toshiko Hirahara JT, Bliacheriene S, Yamaguchi ET, Rizzo Rosa MC, Capel Cardoso MMS. Post-cesarean section analgesia with low spinal morphine doses and systemic nonsteroidal anti-inflammatory drug: Diclofenac versus ketoprofen. Revista Brasileira de Anestesiologia. 2003; 53(6):737-742

1264. Toussaint S, Maidl J, Schwagmeier R, Striebel HW. Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief. Canadian Journal of Anaesthesia. 2000; 47(4):299-302

1265. Treskatsch S, Klambeck M, Mousa SA, Kopf A, Schafer M. Influence of high-dose intraoperative remifentanil with or without amantadine on postoperative pain intensity and morphine consumption in major abdominal surgery patients: a randomised trial. European Journal of Anaesthesiology. 2014; 31(1):41-9

1266. Tsang J, Brush B. Patient-controlled analgesia in postoperative cardiac surgery. Anaesthesia and Intensive Care. 1999; 27(5):464-70

1267. Tsaousi GG, Logan SW, Bilotta F. Postoperative pain control following craniotomy: A systematic review of recent clinical literature. Pain Practice. 2017; 17(7):968-981

1268. Tsui SL, Lee DK, Ng KF, Chan TY, Chan WS, Lo JW. Epidural infusion of bupivacaine 0.0625% plus fentanyl 3.3 micrograms/ml provides better postoperative analgesia than patient-controlled analgesia with intravenous morphine after gynaecological laparotomy. Anaesthesia and Intensive Care. 1997; 25(5):476-81

1269. Tuman KJ, Keane DM, Spiess BD, McCarthy RJ, Silins AI, Ivankovich AD. Effects of high-dose fentanyl on fluid and vasopressor requirements after cardiac surgery. Journal of Cardiothoracic Anesthesia. 1988; 2(4):419-29

1270. Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesthesia and Analgesia. 1991; 73(6):696-704

1271. Tunc M, Gunal H, Bilgili T, Ulus F, Tunc H, Savkilioglu E. The effect of TENS on epidural patient controlled analgesia with tramadol for postthoracotomy pain relief. Turkish Journal of Anaesthesiology and Reanimation. 2002; 30(7):315-321

1272. Tuncali B, Pekcan YO, Celebi A, Zeyneloglu P. Addition of low-dose ketamine to midazolam-fentanyl-propofol-based sedation for colonoscopy: a randomized, double-blind, controlled trial. Journal of Clinical Anesthesia. 2015; 27(4):301-6

1273. Tuncel G, Ozalp G, Savli S, Canoler O, Kaya M, Kadiogullari N. Epidural ropivacaine or sufentanil-ropivacaine infusions for post-thoracotomy pain. European Journal of Cardio-Thoracic Surgery. 2005; 28(3):375-9

1274. Tuncer S, Bariskaner H, Reisli R, Sarkilar G, icekci F, Otelcioglu S. Effect of gabapentin on postoperative pain: A randomized, placebo-controlled clinical study. The Pain Clinic. 2005; 17(1):95-99

1275. Turan A, Karamanlioglu B, Memis D, Hamamcioglu MK, Tukenmez B, Pamukcu Z et al. Analgesic effects of gabapentin after spinal surgery. Anesthesiology. 2004; 100(4):935-8

1276. Turan A, Karamanlioglu B, Memis D, Usar P, Pamukcu Z, Ture M. The analgesic effects of gabapentin after total abdominal hysterectomy. Anesthesia and Analgesia. 2004; 98(5):1370-3

1277. Turan A, White PF, Karamanlioglu B, Memis D, Tasdogan M, Pamukcu Z et al. Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. Anesthesia and Analgesia. 2006; 102(1):175-81

1278. Ture H, Sayin M, Karlikaya G, Bingol CA, Aykac B, Ture U. The analgesic effect of gabapentin as a prophylactic anticonvulsant drug on postcraniotomy pain: a prospective randomized study. Anesthesia and Analgesia. 2009; 109(5):1625-31

1279. Turunen P, Carpelan-Holmstrom M, Kairaluoma P, Wikstrom H, Kruuna O, Pere P et al. Epidural analgesia diminished pain but did not otherwise improve enhanced recovery after laparoscopic sigmoidectomy: a prospective randomized study. Surgical Endoscopy. 2009; 23(1):31-7

1280. Tuzuner Oncul AM, Yazicioglu D, Alanoglu Z, Demiralp S, Ozturk A, Ucok C. Postoperative analgesia in impacted third molar surgery: the role of preoperative diclofenac sodium, paracetamol and lornoxicam. Medical Principles and Practice. 2011; 20(5):470-6

1281. Twersky RS, Jamerson B, Warner DS, Fleisher LA, Hogue S. Hemodynamics and emergence profile of remifentanil versus fentanyl prospectively compared in a large population of surgical patients. Journal of Clinical Anesthesia. 2001; 13(6):407-416

1282. Tzortzopoulou A, McNicol ED, Cepeda MS, Francia MB, Farhat T, Schumann R. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD007126. DOI: 10.1002/14651858.CD007126.pub2.

1283. Ucak A, Onan B, Sen H, Selcuk I, Turan A, Yilmaz AT. The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2011; 25(5):824-9

1284. Ulm M, Watson CH, ElNaggar AC, Tillmanns T, Daily LR. A randomized controlled trial comparing the efficacy of perioperative celecoxib versus ketorolac for perioperative pain control. Gynecologic Oncology. 2017; 145(Suppl 1):16-17

1285. Ulm MA, ElNaggar AC, Tillmanns TD. Celecoxib versus ketorolac following robotic hysterectomy for the management of postoperative pain: An open-label randomized control trial. Gynecologic Oncology. 2018; 151(1):124-128

1286. Uluer MS, Topal A, Tavlan A, Erol A, Kilicaslan A, Otelcioglu S. Comparison of hemodynamics recovery profile and costs of remifentanil versus fentanyl-based sevoflurane anesthesia. Turkiye Klinikleri Journal of Medical Sciences. 2012; 32(3):707-714

1287. Unlugenc H, Gunduz M, Ozalevli M, Akman H. A comparative study on the analgesic effect of tramadol, tramadol plus magnesium, and tramadol plus ketamine for postoperative pain management after major abdominal surgery. Acta Anaesthesiologica Scandinavica. 2002; 46(8):1025-30

1288. Unlugenc H, Ozalevli M, Guler T, Isik G. Postoperative pain management with intravenous patient-controlled morphine: comparison of the effect of adding magnesium or ketamine. European Journal of Anaesthesiology. 2003; 20(5):416-21

1289. Unlugenc H, Vardar MA, Tetiker S. A comparative study of the analgesic effect of patient-controlled morphine, pethidine, and tramadol for postoperative pain management after abdominal hysterectomy. Anesthesia and Analgesia. 2008; 106(1):309-12

1290. Urban MK, Jules-Elysee K, Urquhart B, Cammisa FP, Boachie-Adjei O. Reduction in postoperative pain after spinal fusion with instrumentation using intrathecal morphine. Spine. 2002; 27(5):535-7

1291. Urban MK, Ya Deau JT, Wukovits B, Lipnitsky JY. Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. HSS Journal. 2008; 4(1):62-5

1292. Uribe AA, Arbona FL, Flanigan DC, Kaeding CC, Palettas M, Bergese SD. Comparing the efficacy of iv ibuprofen and ketorolac in the management of

postoperative pain following arthroscopic knee surgery. A randomized double-blind active comparator pilot study. Frontiers in Surgery. 2018; 5:59

1293. Vaghadia H, McLeod DH, Mitchell GW, Merrick PM, Chilvers CR. Small-dose hypobaric lidocaine-fentanyl spinal anesthesia for short duration outpatient laparoscopy. I. A randomized comparison with conventional dose hyperbaric lidocaine. Anesthesia and Analgesia. 1997; 84(1):59-64

1294. Vahedi P, Shimia M, Aghamohammadi D, Mohajernezhadfard Z, Shoeibi A, Lotfinia I et al. Does preemptive gabapentin reduce morphine consumption and remaining leg pain after lumbar discectomy? Neurosurgery Quarterly. 2011; 21(2):114–120

1295. Vaidya AB, Sheth MS, Manghani KK, Shroff P, Vora KK, Sheth UK. Double blind trial of mefenamic acid, aspirin and placebo in patients with post-operative pain. Indian Journal of Medical Sciences. 1974; 28(12):532-6

1296. Valairucha S, Maboonvanon P, Napachoti T, Sirivanasandha B, Suraseranuvongse S. Cost-effectiveness of thoracic patient-controlled epidural analgesia using bupivacaine with fentanyl vs. bupivacaine with morphine after thoracotomy and upper abdominal surgery. Journal of the Medical Association of Thailand. 2005; 88(7):921-927

1297. Van Bergen WS, North WC, Karp M. Effect of dextro propoxyphene, meperidine, and codeine on postoperative pain. JAMA. 1960; 172(13):1372-1375

1298. Van Daele DJ, Bodeker KL, Trask DK. Celecoxib versus placebo in tonsillectomy: A prospective, randomized, double-blind placebo-controlled trial. Annals of Otology, Rhinology and Laryngology. 2016; 125(10):785-800

1299. van den Nieuwenhuyzen MC, Burm AG, Vletter AA, Stienstra R, van Kleef JW. Epidural vs. intravenous infusion of alfentanil in the management of postoperative pain following laparotomies. Acta Anaesthesiologica Scandinavica. 1996; 40(9):1112-8

1300. van den Nieuwenhuyzen MC, Engbers FH, Burm AG, Vletter AA, van Kleef JW, Bovill JG. Computer-controlled infusion of alfentanil versus patient-controlled administration of morphine for postoperative analgesia: a double-blind randomized trial. Anesthesia and Analgesia. 1995; 81(4):671-9

1301. van den Nieuwenhuyzen MC, Stienstra R, Burm AG, Vletter AA, van Kleef JW. Alfentanil as an adjuvant to epidural bupivacaine in the management of postoperative pain after laparotomies: lack of evidence of spinal action. Anesthesia and Analgesia. 1998; 86(3):574-8

1302. Van der Auwera D, Verborgh C, Camu F. Analgesic and cardiorespiratory effects of epidural sufentanil and morphine in humans. Anesthesia and Analgesia. 1987; 66(10):999-1003

1303. Van Elstraete AC, Lebrun T, Sandefo I, Polin B. Ketamine does not decrease postoperative pain after remifentanil-based anaesthesia for tonsillectomy in adults. Acta Anaesthesiologica Scandinavica. 2004; 48(6):756-60

1304. Van Elstraete AC, Tirault M, Lebrun T, Sandefo I, Bernard JC, Polin B et al. The median effective dose of preemptive gabapentin on postoperative morphine consumption after posterior lumbar spinal fusion. Anesthesia and Analgesia. 2008; 106(1):305-308

1305. van Haagen MHM, Verburg H, Hesseling B, Coors L, van Dasselaar NT, Langendijk PNJ et al. Optimizing the dose of local infiltration analgesia and gabapentin for total

knee arthroplasty, a randomized single blind trial in 128 patients. Knee. 2018; 25(1):153-160

1306. van Helmond N, Steegers MA, Filippini-de Moor GP, Vissers KC, Wilder-Smith OH. Hyperalgesia and persistent pain after breast cancer surgery: A prospective randomized controlled trial with perioperative COX-2 inhibition. PloS One. 2016; 11(12):e0166601

1307. van Lersberghe C, Camu F, de Keersmaecker E, Sacre S. Continuous administration of fentanyl for postoperative pain: a comparison of the epidural, intravenous, and transdermal routes. Journal of Clinical Anesthesia. 1994; 6(4):308-314

1308. van Steenberghe D, Verbist D, Quirynen M, Thevissen E. Double-blind comparison of the analgesic potency of ciramadol, codeine and placebo against postsurgical pain in ambulant patients. European Journal of Clinical Pharmacology. 1986; 31(3):355-8

1309. Vasigh A, Najafi F, Khajavikhan J, Jaafarpour M, Khani A. Comparing gabapentin and celecoxib in pain management and complications after laminectomy: A randomized double-blind clinical trial. Iranian Red Crescent Medical Journal. 2016; 18(2):e34559

1310. Verborgh C, Van der Auwera D, Noorduin H, Camu F. Epidural sufentanil for post-operative pain relief: effects of adrenaline. European Journal of Anaesthesiology. 1988; 5(3):183-91

1311. Verma RK, Rao R, Ohri A, Singha D. Comparison of intramuscular lornoxicam and diclofenac sodium for pre- emptive analgesia in patients undergoing open cholecystectomy. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2015; 6(1):1054-1060

1312. Verschraegen R, Rolly G. Double blind study of meptazinol versus pentazocine and placebo in postoperative pain treatment. Acta Anaesthesiologica Belgica. 1979; 30(4):255-64

1313. Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. Anaesthesia. 1992; 47(4):291-6

1314. Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain following abdominal surgery. European Journal of Anaesthesiology. 1995; 12(3):265-71

1315. Villesen HH, Banning AM, Petersen RH, Weinelt S, Poulsen JB, Hansen SH et al. Pharmacokinetics of morphine and oxycodone following intravenous administration in elderly patients. Therapeutics and Clinical Risk Management. 2007; 3(5):961-967

1316. Viscomi CM, Friend A, Parker C, Murphy T, Yarnell M. Ketamine as an adjuvant in lidocaine intravenous regional anesthesia: a randomized, double-blind, systemic control trial. Regional Anesthesia and Pain Medicine. 2009; 34(2):130-3

1317. Viscusi ER, Frenkl TL, Hartrick CT, Rawal N, Kehlet H, Papanicolaou D et al. Perioperative use of etoricoxib reduces pain and opioid side-effects after total abdominal hysterectomy: a double-blind, randomized, placebo-controlled phase III study. Current Medical Research and Opinion. 2012; 28(8):1323-35

1318. Viscusi ER, Gimbel JS, Halder AM, Snabes M, Brown MT, Verburg KM. A multiple-day regimen of parecoxib sodium 20 mg twice daily provides pain relief after total hip arthroplasty. Anesthesia and Analgesia. 2008; 107(2):652-60

1319. Viscusi ER, Manvelian GZ. A randomized study of the serum pharmacokinetics of lower thoracic extended-release epidural morphine (DepoDur) after lidocaine-epinephrine test dose administration in patients undergoing upper abdominal surgery.

International Journal of Clinical Pharmacology and Therapeutics. 2009; 47(11):659-70

1320. von Ungern-Sternberg BS, Regli A, Reber A, Schneider MC. Effect of obesity and thoracic epidural analgesia on perioperative spirometry. British Journal of Anaesthesia. 2005; 94(1):121-7

1321. Vora KS, Shah VR, Patel B, Parikh GP, Butala BP. Postoperative analgesia with epidural opioids after cesarean section: comparison of sufentanil, morphine and sufentanil-morphine combination. Journal of Anaesthesiology Clinical Pharmacology. 2012; 28(4):491-5

1322. Vorsanger GJ, Klopfer AM, Xiang J, Benson CJ, Moskovitz BL, Rosenthal NR. Immediate-release tapentadol or oxycodone for treatment of acute postoperative pain after elective arthroscopic shoulder surgery: a randomized, phase IIIb study. Journal of Opioid Management. 2013; 9(4):281-290

1323. Wade WE, Spruill WJ. Tapentadol hydrochloride: a centrally acting oral analgesic. Clinical Therapeutics. 2009; 31(12):2804-18

1324. Waikakul W, Chalachewa T, Tantisirin N, Suranutkarin P-e, Saengpetch N. Combination of gabapentin and celecoxib for analgesia after major orthopedic surgery: a randomized, controlled trial. Asian Biomedicine. 2011; 5(1):101-110

1325. Walder B, Schafer M, Henzi I, Tramer MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. Acta Anaesthesiologica Scandinavica. 2001; 45(7):795-804

1326. Walton GM, Rood JP, Snowdon AT, Rickwood D. Ketorolac and diclofenac for postoperative pain relief following oral surgery. British Journal of Oral and Maxillofacial Surgery. 1993; 31(3):158-60

1327. Wang F, Shen X, Liu Y, Xu S, Guo X. Continuous infusion of butorphanol combined with intravenous morphine patient-controlled analgesia after total abdominal hysterectomy: a randomized, double-blind controlled trial. European Journal of Anaesthesiology. 2009; 26(1):28-34

1328. Wang H, Gargano C, Lukac S, Jackson A, Beals C, Smiley P et al. An enhanced bunionectomy model as a potential tool for early decision-making in the development of new analgesics. Advances in Therapy. 2010; 27(12):963-80

1329. Wang J, Fu Y, Yuan T, Wang N. Comparison of postoperative analgesic requirements in living donors and patients undergoing similar surgical procedures. Transplantation Proceedings. 2015; 47(6):1896-900

1330. Wang L, Dong Y, Zhang J, Tan H. The efficacy of gabapentin in reducing pain intensity and postoperative nausea and vomiting following laparoscopic cholecystectomy: A meta-analysis. Medicine. 2017; 96(37):e8007

1331. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. Canadian Journal of Anaesthesia. 2016; 63(3):311-25

1332. Wang M, She SZ, Chen CL, Xu XB, Xie XQ. Application study of patient-controlled epidural analgesia in peri-interventional uterine arterial embolization for uterine myomata. Journal of interventional radiology. 2006; 15(8):483-486

1333. Wang N, Zhou H, Song X, Wang J. Comparison of oxycodone and sufentanil for patient-controlled intravenous analgesia after laparoscopic radical gastrectomy: A

randomized double-blind clinical trial. Anesthesia Essays and Researches. 2016; 10(3):557-560

1334. Wang X, Xie H, Wang G. Improved postoperative analgesia with coadministration of preoperative epidural ketamine and midazolam. Journal of Clinical Anesthesia. 2006; 18(8):563-569

1335. Wanna O, Werawatganon T, Piriyakitphaiboon S, Taesiri B. A comparison of propofol and ketamine as induction agents for cesarean section. Journal of the Medical Association of Thailand. 2004; 87(7):774-9

1336. Waris S, Firdaus R, Mumtaz MH. Comparative efficacy and safety of tramol, pethidine and buprenorphine for severe post-operative pain. Specialist. 1994; 10(3):197-202

1337. Warrender WJ, Syed UAM, Hammoud S, Emper W, Ciccotti MG, Abboud JA et al. Pain management after outpatient shoulder arthroscopy: A systematic review of randomized controlled trials. American Journal of Sports Medicine. 2017; 45(7):1676-1686

1338. Wasey J, Derry S, Moore R, McQuay H. Single dose oral diflunisal for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD007440. DOI: 10.1002/14651858.CD007440.pub2.

1339. Watanabe H. Eptazocine (ST-2121(l)), a new analgesic: double blind comparison with pentazocine in patients of urologic postoperative pain. Japanese Pharmacology and Therapeutics. 1982; 10(6):3513-3524

1340. Watanabe H. Eptazocine, a new analgesic-double blind comparison with pentazocine in patients of urologic postoperative pain. Japanese pharmacology & therapeutics. 1982; 10(6):569-580

1341. Watcha MF, Issioui T, Klein KW, White PF. Costs and effectiveness of rofecoxib, celecoxib, and acetaminophen for preventing pain after ambulatory otolaryngologic surgery. Anesthesia and Analgesia. 2003; 96(4):987-94

1342. Wattchow DA, De Fontgalland D, Bampton PA, Leach PL, McLaughlin K, Costa M. Clinical trial: the impact of cyclooxygenase inhibitors on gastrointestinal recovery after major surgery - a randomized double blind controlled trial of celecoxib or diclofenac vs. placebo. Alimentary Pharmacology and Therapeutics. 2009; 30(10):987-98

1343. Webb AR, Skinner BS, Leong S, Kolawole H, Crofts T, Taverner M et al. The addition of a small-dose ketamine infusion to tramadol for postoperative analgesia: a double-blinded, placebo-controlled, randomized trial after abdominal surgery. Anesthesia and Analgesia. 2007; 104(4):912-7

1344. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesthesia and Analgesia. 2003; 96(3):789-95

1345. Welchew EA, Breen DP. Patient-controlled on-demand epidural fentanyl. A comparison of patient-controlled on-demand fentanyl delivered epidurally or intravenously. Anaesthesia. 1991; 46(6):438-41

1346. Welchew EA, Hosking J. Patient-controlled postoperative analgesia with alfentanil. Adaptive, on-demand intravenous alfentanil or pethidine compared double-blind for postoperative pain. Anaesthesia. 1985; 40(12):1172-7

1347. Weller R, Rosenblum M, Conard P, Gross JB. Comparison of epidural and patient-controlled intravenous morphine following joint replacement surgery. Canadian Journal of Anaesthesia. 1991; 38(5):582-6

1348. Werawatganon T, Charuluxananan S. WITHDRAWN: Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD004088. DOI: 10.1002/14651858.CD004088.pub3.

1349. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD004088. DOI: 10.1002/14651858.CD004088.pub2.

1350. Wheatley RG, Somerville ID, Sapsford DJ, Jones JG. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. British Journal of Anaesthesia. 1990; 64(3):267-75

1351. White I, Ghinea R, Avital S, Chazan S, Dolkart O, Weinbroum AA. Morphine at "sub-analgesic" background infusion rate plus low-dose PCA bolus control pain better and is as safe as twice a bolus-only PCA regimen: a randomized, double blind study. Pharmacological Research. 2012; 66(2):185-91

1352. White MJ, Berghausen EJ, Dumont SW, Tsueda K, Schroeder JA, Vogel RL et al. Side effects during continuous epidural infusion of morphine and fentanyl. Canadian Journal of Anaesthesia. 1992; 39(6):576-82

1353. White PF, Sacan O, Tufanogullari B, Eng M, Nuangchamnong N, Ogunnaike B. Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. Canadian Journal of Anaesthesia. 2007; 54(5):342-8

1354. White PF, Tang J, Wender RH, Zhao M, Time M, Zaentz A et al. The effects of oral ibuprofen and celecoxib in preventing pain, improving recovery outcomes and patient satisfaction after ambulatory surgery. Anesthesia and Analgesia. 2011; 112(2):323-9

1355. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesthesia and Analgesia. 2009; 108(4):1140-5

1356. Wilde GP, Whitaker AJ, Moulton A. Epidural buprenorphine for pain relief after spinal decompression. Journal of Bone and Joint Surgery - British Volume. 1988; 70(3):448-50

1357. Wilder-Smith OH, Arendt-Nielsen L, Gaumann D, Tassonyi E, Rifat KR. Sensory changes and pain after abdominal hysterectomy: a comparison of anesthetic supplementation with fentanyl versus magnesium or ketamine. Anesthesia and Analgesia. 1998; 86(1):95-101

1358. Winter DC, Dozois EJ, Pemberton JH. Postoperative thoracic epidural anesthesia in gastrointestinal surgery: Outcomes, quality of Life, and current controversies. Current Drug Therapy. 2007; 2(1):75-77

1359. Wittels B, Glosten B, Faure EA, Moawad AH, Ismail M, Hibbard J et al. Opioid antagonist adjuncts to epidural morphine for postcesarean analgesia: maternal outcomes. Anesthesia and Analgesia. 1993; 77(5):925-32

1360. Wolff J, Carl P, Crawford ME. Epidural buprenorphine for postoperative analgesia. A controlled comparison with epidural morphine. Anaesthesia. 1986; 41(1):76-9

1361. Wong CS, Lu CC, Cherng CH, Ho ST. Pre-emptive analgesia with ketamine, morphine and epidural lidocaine prior to total knee replacement. Canadian Journal of Anaesthesia. 1997; 44(1):31-37

1362. Wong JO, Tan TD, Cheu NW, Wang YR, Liao CH, Chuang FH et al. Comparison of the efficacy of parecoxib versus ketorolac combined with morphine on patient-controlled analgesia for post-cesarean delivery pain management. Acta Anaesthesiologica Taiwanica 2010; 48(4):174-7

1363. Wongyingsinn M, Baldini G, Stein B, Charlebois P, Liberman S, Carli F. Spinal analgesia for laparoscopic colonic resection using an enhanced recovery after surgery programme: better analgesia, but no benefits on postoperative recovery: a randomized controlled trial. British Journal of Anaesthesia. 2012; 108(5):850-6

1364. Woo JH, Kim YJ, Baik HJ, Han JI, Chung RK. Does intravenous ketamine enhance analgesia after arthroscopic shoulder surgery with ultrasound guided single-injection interscalene block?: a randomized, prospective, double-blind trial. Journal of Korean Medical Science. 2014; 29(7):1001-6

1365. Wrench IJ, Cavill G, Ward JE, Crossley AW. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. British Journal of Anaesthesia. 1997; 79(4):541-2

1366. Wu CL, Cohen SR, Richman JM, Rowlingson AJ, Courpas GE, Cheung K et al. Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a meta-analysis. Anesthesiology. 2005; 103(5):1079-88; quiz 1109-10

1367. Wu CT, Yeh CC, Yu JC, Lee MM, Tao PL, Ho ST et al. Pre-incisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. Acta Anaesthesiologica Scandinavica. 2000; 44(1):63-8

1368. Wu HY, Gong CS, Lin SP, Chang KY, Tsou MY, Ting CK. Predicting postoperative vomiting among orthopedic patients receiving patient-controlled epidural analgesia using SVM and LR. Scientific Reports. 2016; 6:27041

1369. Wuethrich PY, Burkhard FC. New perioperative fluid and pharmacologic management protocol results in reduced blood loss, faster return of bowel function, and overall recovery. Current Urology Reports. 2015; 16:17

1370. Wulf H, Biscoping J, Beland B, Bachmann-Mennenga B, Motsch J. Ropivacaine epidural anesthesia and analgesia versus general anesthesia and intravenous patient-controlled analgesia with morphine in the perioperative management of hip replacement. Ropivacaine Hip Replacement Multicenter Study Group. Anesthesia and Analgesia. 1999; 89(1):111-6

1371. Xie H, Wang X, Liu G, Wang G. Analgesic effects and pharmacokinetics of a low dose of ketamine preoperatively administered epidurally or intravenously. Clinical Journal of Pain. 2003; 19(5):317-22

1372. Xie K, Zhang W, Fang W, Lian Y, Lin S, Fang J. The analgesic efficacy of oxycodone hydrochloride versus fentanyl during outpatient artificial abortion operation: A randomized trial. Medicine. 2017; 96(26):e7376

1373. Xiude C, Feng L, Peng L. Effect of gabapentin on patient controlled intravenous analgesia after modified radical mastectomy. Chinese Journal of Postgraduates of Medicine. 2010; (33):13-16

1374. Xudong X. The efficacy of gabapentin in the laparoscopic cholecystectomy. Journal of Clinical Anesthesiology. 2008; 24:1083-1087

1375. Xue ZG, Bai L, Jiang H. Combined epidural block with general anesthesia in patients with chronic obstructive pulmonary disease. Journal of Shanghai Medical University. 2000; 27(4):302-305+323

1376. Xuliang W, Xiaoning Y, Ling Q. Application of preemptive analgesia of gabapentin in laparoscopic cholecystectomy. Journal of Southeast China National Defence Medical Science. 2009; 2009:50-52

1377. Yaddanapudi LN, Wig J, Singh B, Tewari MK. Comparison of efficacy and side effects of epidural tramadol and morphine in patients undergoing laminectomy: a repeated dose study. Neurology India. 2000; 48(4):398-400

1378. YaDeau JT, Lin Y, Mayman DJ, Goytizolo EA, Alexiades MM, Padgett DE et al. Pregabalin and pain after total knee arthroplasty: a double-blind, randomized, placebo-controlled, multidose trial. British Journal of Anaesthesia. 2015; 115(2):285-93

1379. YaDeau JT, Paroli L, Fields KG, Kahn RL, LaSala VR, Jules-Elysee KM et al. Addition of dexamethasone and buprenorphine to bupivacaine sciatic nerve block: A randomized controlled trial. Regional Anesthesia and Pain Medicine. 2015; 40(4):321-9

1380. Yadeau JT, Paroli L, Kahn RL, Jules-Elysee KM, Lasala VR, Liu SS et al. Addition of pregabalin to multimodal analgesic therapy following ankle surgery: a randomized double-blind, placebo-controlled trial. Regional Anesthesia and Pain Medicine. 2012; 37(3):302-7

1381. Yaghoubi S, Pourfallah R, Barikani A, Kayalha H. The postoperative analgesic effect of morphine and paracetamol in the patients undergoing laparotomy, using PCA method. Global Journal of Health Science. 2013; 6(1):207-14

1382. Yalcin N, Uzun ST, Reisli R, Borazan H, Otelcioglu S. A comparison of ketamine and paracetamol for preventing remifentanil induced hyperalgesia in patients undergoing total abdominal hysterectomy. International Journal of Medical Sciences. 2012; 9(5):327-33

1383. Yamashita K, Fukusaki M, Ando Y, Fujinaga A, Tanabe T, Terao Y et al. Preoperative administration of intravenous flurbiprofen axetil reduces postoperative pain for spinal fusion surgery. Journal of Anesthesia. 2006; 20(2):92-5

1384. Yamauchi M, Asano M, Watanabe M, Iwasaki S, Furuse S, Namiki A. Continuous low-dose ketamine improves the analgesic effects of fentanyl patient-controlled analgesia after cervical spine surgery. Anesthesia and Analgesia. 2008; 107(3):1041-4

1385. Yanagida H. Double-blind studies of stadol (butorphanol tartrate)/pentazocine for postoperative pain. Japanese Journal of Anesthesiology. 1980; 29(3):237-239

1386. Yanagidate F, Dohi S. Epidural oxycodone or morphine following gynaecological surgery. British Journal of Anaesthesia. 2004; 93(3):362-7

1387. Yang HJ. The preemptive analgesic effect of ketamine used with fentanyl in epidural anesthesia. Korean Journal of Anesthesiology. 1999; 36(1):112-117

1388. Yang L, Du S, Sun Y. Intravenous acetaminophen as an adjunct to multimodal analgesia after total knee and hip arthroplasty: A systematic review and meta-analysis. International Journal of Surgery. 2017; 47:135-146

1389. Yang L, Zhang J, Zhang Z, Zhang C, Zhao D, Li J. Preemptive analgesia effects of ketamine in patients undergoing surgery. A meta-analysis. Acta Cirurgica Brasileira. 2014; 29(12):819-25

1390. Yang SA, Kim KS, Kang HY. Oxycodone vs. fentanyl in the treatment of early post-operative pain after total knee replacement: randomized controlled trial. Anesthesiology and Pain Medicine. 2016; 11(4):349-353

1391. Yang TC, Chan KH, Shu CC, Jong HR, Tswei TS, Lee TY. Postoperative pain relief: lumbar and thoracic epidural morphine in thoracotomy. Chinese Medical Journal. 1993; 52(4):235-40

1392. Yao Z, Shen C, Zhong Y. Perioperative pregabalin for acute pain after gynecological surgery: A meta-analysis. Clinical Therapeutics. 2015; 37(5):1128-35

1393. Yardeni IZ, Shavit Y, Bessler H, Mayburd E, Grinevich G, Beilin B. Comparison of postoperative pain management techniques on endocrine response to surgery: a randomised controlled trial. International Journal of Surgery. 2007; 5(4):239-43

1394. Yarmush J, D'Angelo R, Kirkhart B, O'Leary C, Pitts MC, 2nd, Graf G et al. A comparison of remifentanil and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifentanil and propofol. Anesthesiology. 1997; 87(2):235-43

1395. Yarnell RW, Polis T, Reid GN, Murphy IL, Penning JP. Patient-controlled analgesia with epidural meperidine after elective cesarean section. Regional Anesthesia. 1992; 17(6):329-33

1396. Yavuz L, Eroglu F, Ozsoy M. The efficacy of intravenous versus epidural tramadol with patient-controlled analgesia (PCA) in gynecologic cancer pain. European Journal of Gynaecological Oncology. 2004; 25(2):215-8

1397. Yazigi A, Abou-Zeid H, Srouji T, Madi-Jebara S, Haddad F, Jabbour K. The effect of low-dose intravenous ketamine on continuous intercostal analgesia following thoracotomy. Annals of Cardiac Anaesthesia. 2012; 15(1):32-8

1398. Ye F, Wu Y, Zhou C. Effect of intravenous ketamine for postoperative analgesia in patients undergoing laparoscopic cholecystectomy: A meta-analysis. Medicine. 2017; 96(51):e9147

1399. Yeganeh Mogadam A, Fazel MR, Parviz S. Comparison of analgesic effect between gabapentin and diclofenac on post-operative pain in patients undergoing tonsillectomy. Archives of Trauma Research. 2012; 1(3):108-11

1400. Yentur EA, Topcu I, Keles GT, Tasyuz T, Sakarya M. Subanalgesic dose of ketamine added to tramadol does not reduce analgesic demand. Turkish Journal of Anaesthesiology and Reanimation. 2004; 32(2):106-112

1401. Yeom JH, Chon MS, Jeon WJ, Shim JH. Peri-operative ketamine with the ambulatory elastometric infusion pump as an adjuvant to manage acute postoperative pain after spinal fusion in adults: a prospective randomized trial. Korean Journal of Anesthesiology. 2012; 63(1):54-8

1402. Yeung J, Gates S, Naidu B, Wilson M, Gao SF. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD009121. DOI: 10.1002/14651858.CD009121.pub2.

1403. Yilmaz C, Coruh T, Yapici N, Yilmaz O, Macika H, Aykac Z. The effects of preemptive analgesia with thoracic epidural on respiratory function tests, pain scores and

hemodynamics in coronary artery bypass graft surgery. Anestezi Dergisi. 2007; 15(1):20-27

1404. Yokota T, Uehara K, Nomoto Y. Intrathecal morphine suppresses NK cell activity following abdominal surgery. Canadian Journal of Anaesthesia. 2000; 47(4):303-8

1405. Yonemura E, Shimada M, Nakamura M, Fukushima K. Influence of intrathecal morphine and buprenorphine on EEG and their analgesic effect. Japanese Journal of Anesthesiology. 1990; 39(4):478-485

1406. Yoon SH, Lee JH, Yoon HS, Kim YH, Na MH, Lim SP. Post-thoracotomy analgesia & ICU length of stay: comparison of thoracic epidrual morphine infusion and lumbar epidural plus intravenous morphine infusion. Korean Journal of Critical Care Medicine. 2007; 22(2):77-82

1407. Yoshimura N, Iida H, Takenaka M, Tanabe K, Yamaguchi S, Kitoh K et al. Effect of postoperative administration of pregabalin for post-thoracotomy pain: a randomized study. Journal of Cardiothoracic and Vascular Anesthesia. 2015; 29(6):1567-72

1408. Yosunkaya A, Tavlan A, Tuncer S, Reıslı R, Topal A, Ökeslı S. Comparison of the effects of intravenous and thoracic epidural patient-controlled analgesia with morphine after upper abdominal surgery. The Pain Clinic. 2003; 15(3):271-279

1409. Young RE. Double-blind placebo controlled oral analgesic comparison of butorphanol andpentazocine in patients with moderate to severe post-operative pain. Journal of International Medical Research. 1977; 5(6):422-8

1410. Young RE. A comparison of analgesic effectiveness of oral butorphanol/acetaminophen, oxycodone/acetaminophen and placebo in hospitalized postsurgical patients. Journal of Medicine. 1979; 10(6):417-28

1411. Young RE, Quigley JJ, Archambault WA, Jr., Gordon LL. Butorphanol/acetaminophen double-blind study in postoperative pain. Journal of Medicine. 1979; 10(4):239-56

1412. Youssef N, Orlov D, Alie T, Chong M, Cheng J, Thabane L et al. What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery?: a meta-analysis of randomized controlled trials. Anesthesia and Analgesia. 2014; 119(4):965-77

1413. Ypsilantis E, Tang TY. Pre-emptive analgesia for chronic limb pain after amputation for peripheral vascular disease: a systematic review. Annals of Vascular Surgery. 2010; 24(8):1139-46

1414. Ysasi A, Calderon E, Wendt T, Gracia N, Torres LM, Llorens R. Efficacy of low doses of ketamine in postoperative analgesia and the use of morphine after myocardial revascularisation surgery. Revista de la Sociedad Espanola del Dolor. 2010; 17(4):190-195

1415. Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. Spine. 2013; 38(22):1947-52

1416. Yu SZ, Xu LX, Liu JY, Png LX. A randomized-blind comparison of efficacy of patient controlled epidural analgesia with combinations of fentanyl and other drugs for postoperative pain. Chinese Journal of Anesthesiology. 1997; 17(4):245-247

1417. Yucel A, Ozturk E, Aydogan MS, Durmus M, Colak C, Ersoy MO. Effects of 2 different doses of pregabalin on morphine consumption and pain after abdominal hysterectomy: a randomized, double-blind clinical trial. Current Therapeutic Research, Clinical and Experimental. 2011; 72(4):173-83

1418. Yun YD, Kim HJ, Choi SJ, Lee JU, Yun SH, Lee SW. The Comparison of Epidural Morphine and Epidural Morphine-Ketamine for Postoperative Pain Relief after Subtotal Gastrectomy. Korean Journal of Anesthesiology. 2000; 39(1):91-97

1419. Yung MC, Chang Y, Lai ST, Tsou MY, Chan KH. Improved postoperative pain relief via preemptive analgesia in relation to heart rate variability for coronary artery bypass grafting: a preliminary report. Chinese Medical Journal. 1997; 60(1):28-35

1420. Zacharias M, Pfeifer MV, Herbison P. Comparison of two methods of intravenous administration of morphine for postoperative pain relief. Anaesthesia and Intensive Care. 1990; 18(2):205-9

1421. Zakine J, Samarcq D, Lorne E, Moubarak M, Montravers P, Beloucif S et al. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesthesia and Analgesia. 2008; 106(6):1856-61

1422. Zakkar M, Frazer S, Hunt I. Is there a role for gabapentin in preventing or treating pain following thoracic surgery? Interactive Cardiovascular and Thoracic Surgery. 2013; 17(4):716-9

1423. Zarauza R, Saez-Fernandez AN, Iribarren MJ, Carrascosa F, Adame M, Fidalgo I et al. A comparative study with oral nifedipine, intravenous nimodipine, and magnesium sulfate in postoperative analgesia. Anesthesia and Analgesia. 2000; 91(4):938-43

1424. Zavareh SM, Kashefi P, Saghaei M, Emami H. Pre emptive analgesia for reducing pain after cholecystectomy: Oral tramadol vs. acetaminophen codeine. Advanced Biomedical Research. 2013; 2:12

1425. Zeedick JF. A double-blind comparison of oral butorphanol and codeine. Current Medical Research and Opinion. 1979; 6(3):178-82

1426. Zeid HA, Siddiqui AK, Elmakarem EFA, Ghonaimy Y, Nafea AA. Comparison between intrathecal morphine with paravertebral patient controlled analgesia using bupivacaine for intraoperative and post-thoracotomy pain relief. Saudi Journal of Anaesthesia. 2012; 6(3):201-206

1427. Zeidan A, Mazoit JX, Ali Abdullah M, Maaliki H, Ghattas T, Saifan A. Median effective dose (ED_{50}) of paracetamol and morphine for postoperative pain: a study of interaction. British Journal of Anaesthesia. 2014; 112(1):118-123

1428. Zejun N, Wei F, Lin L, He D, Haichen C. Improvement of recovery parameters using patient-controlled epidural analgesia for video-assisted thoracoscopic surgery lobectomy in enhanced recovery after surgery: A prospective, randomized single center study. Thoracic Cancer. 2018; 9(9):1174-1179

1429. Zelcer J, White PF, Chester S, Paull JD, Molnar R. Intraoperative patient-controlled analgesia: an alternative to physician administration during outpatient monitored anesthesia care. Anesthesia and Analgesia. 1992; 75(1):41-4

1430. Zgaia AO, Irimie A, Sandesc D, Vlad C, Lisencu C, Rogobete A et al. The role of ketamine in the treatment of chronic cancer pain. Clujul Medical. 2015; 88(4):457-61

1431. Zhai L, Song Z, Liu K. The effect of gabapentin on acute postoperative pain in patients undergoing total knee arthroplasty: A meta-analysis. Medicine. 2016; 95(20):e3673

1432. Zhang DG, Peng K, Chen L, Peng J, Xing F, Wang GL. Gabapentin can decrease pain intensity for patients undergoing total knee arthroplasty: A systematic review

meta-analysis. International Journal of Clinical and Experimental Medicine. 2016; 9(8):15105-15114

1433. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. British Journal of Anaesthesia. 2011; 106(4):454-62

1434. Zhang S, Paul J, Nantha-Aree M, Buckley N, Shahzad U, Cheng J et al. Empirical comparison of four baseline covariate adjustment methods in analysis of continuous outcomes in randomized controlled trials. Clinical Epidemiology. 2014; 6:227-35

1435. Zhang S, Paul J, Nantha-Aree M, Buckley N, Shahzad U, Cheng J et al. Reanalysis of morphine consumption from two randomized controlled trials of gabapentin using longitudinal statistical methods. Journal of Pain Research. 2015; 8:79-85

1436. Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain--a meta-analysis. Journal of Clinical Pharmacy and Therapeutics. 1996; 21(4):261-82

1437. Zhang Z, Zhu W, Zhu L, Du Y. Efficacy of celecoxib for pain management after arthroscopic surgery of hip: a prospective randomized placebo-controlled study. European journal of orthopaedic surgery & traumatologie. 2014; 24(6):919-23

1438. Zhao H, Feng Y, Wang Y, Yang B, Xing Z. Comparison of different loading dose of celecoxib on postoperative anti-inflammation and analgesia in patients undergoing endoscopic nasal surgery-200 mg is equivalent to 400 mg. Pain Medicine. 2011; 12(8):1267-75

1439. Zhou X, Zhang C, Wang M, Yu L, Yan M. Dezocine for preventing postoperative pain: A meta-analysis of randomized controlled trials. PloS One. 2015; 10(8):e0136091

1440. Zhou XN. Preoperative use of gabapentin for postoperative fentanyl analgesia administration in patients with total knee replacement. Jikang Bidu. 2013; 6:428

1441. Zhu J, Xie H, Zhang L, Chang L, Chen P. Efficiency and safety of ketamine for pain relief after laparoscopic cholecystectomy: A meta-analysis from randomized controlled trials. International Journal of Surgery. 2018; 49:1-9

1442. Zhu Y, Yao R, Li Y, Wu C, Heng L, Zhou M et al. Protective effect of celecoxib on early postoperative cognitive dysfunction in geriatric patients. Frontiers in Neurology. 2018; 9:633

1443. Zhu YZ, Yao R, Zhang Z, Xu H, Wang LW. Parecoxib prevents early postoperative cognitive dysfunction in elderly patients undergoing total knee arthroplasty: A double-blind, randomized clinical consort study. Medicine. 2016; 95(28):e4082

1444. Zittel TT, Razavi D, Papp A, Lundberg K. Increased risk for complications after colorectal surgery with selective cyclo-oxygenase 2 inhibitor etoricoxib. Diseases of the Colon and Rectum. 2013; 56(6):761-7

1445. Ziyaeifard M, Mehrabanian MJ, Faritus SZ, Khazaei Koohpar M, Ferasatkish R, Hosseinnejad H et al. Premedication with oral pregabalin for the prevention of acute postsurgical pain in coronary artery bypass surgery. Anesthesiology and Pain Medicine. 2015; 5(1):e24837

1446. Zotou A, Siampalioti A, Tagari P, Paridis L, Kalfarentzos F, Filos KS. Does epidural morphine loading in addition to thoracic epidural analgesia benefit the postoperative management of morbidly obese patients undergoing open bariatric surgery? A pilot study. Obesity Surgery. 2014; 24(12):2099-108

1447. Zucker TP, Flesche CW, Germing U, Schroter S, Willers R, Wolf HH et al. Patient-controlled versus staff-controlled analgesia with pethidine after allogeneic bone marrow transplantation. Pain. 1998; 75(2-3):305-12

1448. Zutshi M, Delaney CP, Senagore AJ, Mekhail N, Lewis B, Connor JT et al. Randomized controlled trial comparing the controlled rehabilitation with early ambulation and diet pathway versus the controlled rehabilitation with early ambulation and diet with preemptive epidural anesthesia/analgesia after laparotomy and intestinal resection. American Journal of Surgery. 2005; 189(3):268-72