National Institute for Health and Care Excellence

Consultation

Perioperative care in adults

[N1] Evidence reviews for managing acute postoperative pain

NICE guideline

Intervention evidence review

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Introduction

Treating post-surgical pain (PSP) has been an established part of perioperative care for decades. PSP management was initially driven by the humanitarian imperative to alleviate suffering, however subsequently additional benefits of effective pain relief were highlighted in attenuating the stress response to surgery and facilitating early mobilisation. Consequently, high quality analgesia has become the cornerstone of modern anaesthetic and surgical practice. Up until the mid-1990's post-operative analgesia was unimodal, and was limited in the main to on demand/ as required administration of intramuscular opioids. Patient Controlled Analgesia (PCA) and epidural analgesia were available for the more major procedures.

In the last few years the concept of administering sufficient analgesia using a multimodal approach to promote the restoration of function 'DrEaMing' (Drinking, Eating and Mobilising) has gained traction. DrEaMing is now one of the 5 Perioperative Quality Improvement Programmes (PQIP) Priorities.

Many preoperative, intraoperative, and postoperative interventions and management strategies are available for managing pain and these need to be tailored to the individual based on factors such as previous pain history, comorbidities, type of surgical procedure and the expected level of pain.

Despite these insights, there remains compelling evidence that pain following surgery is often poorly managed, with up to 40% of patients reporting severe pain that negatively impacts on their recovery. Poorly controlled PSP is also a risk factor for persistent post-surgical pain (PPSP). PPSP effects 5-60% of patients after all types of surgery and can be a severe and debilitating entity. Furthermore, a carefully implemented pain management plan is important if persistent post-operative pain medication use it to be avoid. This report looks at the evidence for the most clinically and cost-effective strategies for managing acute post-operative pain, evaluating the role or delivery of simple analgesics, opioids, ketamine and neuropathic nerve stabilisers across eight reviews. Due to the wide range of pharmacological interventions available we have concentrated on those where there is a variation in current practice and/or where the is uncertainy regarding the benefits and harms.

1 Simple Analgesics:Paracetamol

1.1 Review question 1: What is the clinical and cost effectiveness of IV paracetamol compared to oral paracetamol given post operatively in managing acute postoperative pain?

1.2 PICO table

For full details see the review protocol in appendices.

Table 1: PICO characteristics of review question

Population	Adults (18 years and older) who have undergone surgery.
Interventions	• IV paracetamol
Comparisons	• Oral paracetamol

Outcomes	CRITICAL:
	• health-related quality of life
	• pain reduction
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• amount of additional medication use
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• adverse events (including respiratory depression, nausea, vomiting)
	IMPORTANT:
	• psychological distress and mental well-being
	• symptom scores
	• functional measures
	• length of stay in intensive care
	• length of stay in hospital
	• hospital readmission

Study design	Randomised controlled trials and systematic reviews of randomised controlled trials.

1.3 Clinical evidence

1.3.1 Included studies

Six randomised controlled trials were included in the review;[65, 98, 151, 171, 187, 188] these are summarised in table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3 and Table 4).

See appendices for the study selection flow chart, study evidence tables, forest plots and GRADE tables.

1.3.2 Excluded studies

See the excluded studies list in appendices.

1.3.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Fenlon 2013[65]	IV 1g paracetamol. (Perfalgan™) plus oral placebo N=65 Oral 1g paracetamol plus IV placebo). N=65	Patients aged 18–65 undergoing at least one lower third molar extraction under general anaesthesia as a day case. Mean age years (range) IV:18.7-54.4 Oral: 18.1-57.7	• Satisfactory pain relief at 1 hour • Pain score at 1 hour • Rescue medication at 1 hour • Time to rescue medication	Oral paracetamol given before induction of anaesthesia and IV paracetamol given intraoperatively after induction of anaesthesia Rescue medication- 50 mg i.v. diclofenac

Jarde 1997[98]	IV propacetamol 2g [= paracetamol (PA) 1g]
	N=108
	
	Oral paracetamol 1g
	N=106
		Patients undergoing a hallux valgus plasty performed with local anaesthesia.
		
		Mean age (SD)
		IV: 52.2 (13)
		Oral: 51.7 (14.5)
		
		France
			• Pain score ≤6 hours
			• Time to rescue medication
			• Adverse events
			  ○ Vomiting
			  ○ Nausea	

Moller 2005[151]	2 g propacetamol (2-min i.v. bolus injection)
	N=50
	
	2g propacetamol (15 min i.v. infusion)
	N=50
		Inpatients aged ≥ 18-50 years undergoing removal of an impacted mandibular third molar (and ipsilateral maxillary third molar if indicated) under standardized local anaesthesia and with moderate to severe pain	• Time to maximum pain relief
			• Adverse events
			  ○ Patients with ≤ 1 adverse events
			  ○ nausea
				Rescue analgesia- ibuprofen 600mg orally

Study	Intervention and comparison	Population	Outcomes	Comments
	oral acetaminophen 1 g N=50	(assessed on a four-point scale) within 4 hours of surgery. Mean age years (range): IV bolus group: 25.6 (20-42) IV infusion group: 24.2 (18-39) Oral group: 23.8 (19-36) Denmark		

O'Neal 2017[171]	1 g IV acetaminophen and oral placebo
	N=57
	
	1 g oral acetaminophen and volume-matched IV normal saline (100 ml).
	N=58
		Patients aged ≥ 18 years undergoing unilateral Total Knee Arthroplasty under spinal anaesthesia
		
		Mean age years (SD):
		IV group: 68 (8.3)
		Oral group: 67 (9.0)
		
		USA
			• Pain score in Post Anaesthesia Care Unit
			  ○ ≤ 6 hours post op
			• Rescue medication: total opiate consumption (IV hydromorphone equivalents)
			  ○ ≤ 6 hours post op
			  ○ > 6 hours- 24 hours post op
				Adjunct to multimodal analgesia regimen:
				The 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 (4-10 mg) intraoperatively at the discretion of the in-room anesthesia provider before surgical incision.
				
				Three arm trial including placebo arm

Study	Intervention and comparison	Population	Outcomes	Comments
Plunkett 2017[187]	2x1,000 mg IV acetaminophen and an oral placebo 2x 1,000 mg oral acetaminophen and IV saline.	Adults (age > 18 years) active undergoing a laparoscopic cholecystectomy ASA I-III USA	• Pain intensity over 24 hours • Pain scores ≤ 4 over 24 hours • Additional medication: total opiate consumption (oral morphine equivalents)	The standard regimen was analgesia (fentanyl and/or hydromorphone) intraoperatively. Postoperative nausea and vomiting prophylaxis with dexamethasone, ondansetron, or both. On discharge, patients were prescribed non acetaminophen -containing oral analgesics.

Politi 2017[188]	IV 1g acetaminophen preoperatively and every 6 hours post operatively for 2 hours
	N=63
	
	Oral 1g acetaminophen preoperatively and then postoperatively every 6 hours
	N=57
		All patients undergoing primary hip or knee arthroplasty.
		
		USA
			• Pain scores at:
			  ○ 4 hours
			  ○ 24 hours
			
			• Amount of additional medication (hydromorphine equivalents):
			  ○ 4 hours
			  ○ 24 hours
				The standard 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 anti-nausea medication. Patients were discharged on percocet 5/325 mg prn and meloxicam 7.5 mg daily.

See appendices for full evidence tables.

1.3.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: IV paracetamol versus oral paracetamol for acute post-operative pain

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IV paracetamol versus oral paracetamol (95% CI)
Pain score at ≤6 hours Lower score is better	363 (3 studies)	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean pain score at 6 hours in the control groups was 5.11	The mean pain score <6 hours in the intervention groups was 0.93 lower (1.27 to 0.59 lower)
Pain score < 4 over 24 hours	67 (1 study)	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.16 (0.72 to 1.86)	Moderate	
				471 per 1000	75 more per 1000 (from 132 fewer to 405 more)
Pain score at 24 hours Lower score is better	120 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain score at 24 hours in the control groups was 3.34	The mean pain score 24 hours in the intervention groups was 0.76 lower (1.69 lower to 0.17 higher)
Summed pain intensity at 6 hours (SPID6) Higher score is better	214 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain intensity at 24 hours (spid6) in the control groups was -153.57	The mean pain intensity at 6 hours (spid6) in the intervention groups was 110.38 higher (6.21 to 214.55 higher)
Summed pain intensity at 24 hours (SPID24) Higher score is better	67 (1 study)	⊕⊕⊖⊖ LOW2 due to imprecision		Result given as mean difference.	The mean pain intensity at 24 hours (spid24) in the intervention groups was 5.73 higher (12.54 lower to 24 higher)
Satisfactory pain relief at 1 hour	128 (1 study)	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.1 (0.6 to 2)	Moderate	
				238 per 1000	24 more per 1000 (from 95 fewer to 238 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IV paracetamol versus oral paracetamol (95% CI)
Requesting rescue medication	128 (1 study)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.52 (0.25 to 1.06)	Moderate	
				277 per 1000	133 fewer per 1000 (from 208 fewer to 17 more)
Total opiate consumption (OME24) Lower score is better	67 (1 study)	⊕⊕⊖⊖ LOW2 due to imprecision		Result given as mean difference.	The mean total opiate consumption (ome24) in the intervention groups was 11.33 lower (44.28 lower to 21.62 higher)
Opiate consumption (hydromorphine equivalents) <6 hours Lower score is better	235 (2 studies)	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean opiate consumption in the control group was 0.61	The mean opiate consumption (hydromorpine equivalents) <6 hours in the intervention groups was 0.06 lower (0.22 lower to 0.1 higher)
Opiate consumption (hydromorphine equivalents) 6-24 hours Lower score is better	235 (2 studies)	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean opiate consumption in the control group was 0.79	The mean opiate consumption (hydromorphine equivalents) 6-24 hours in the intervention groups was 0.01 higher (0.09 lower to 0.12 higher)
Number of participants with adverse events (Infusion paracetamol)	100 (1 study)	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 1.81 (1.26 to 2.6)	Moderate	
				420 per 1000	340 more per 1000 (from 109 more to 672 more)
Number of participants with adverse events (bolus IV paracetamol)	100 (1 study)	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 2.33 (1.68 to 3.24)	Moderate	
				420 per 1000	559 more per 1000 (from 286 more to 941 more)
Nausea (infusion paracetamol)	100 (1 study)	⊕⊕⊖⊖ LOW1 due to risk of bias	Peto OR 9.74 (3.05 to 31.05)	Moderate	
				0 per 100	Not estimable
Nausea (bolus IV paracetamol)	314	⊕⊖⊖⊖	Peto OR	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IV paracetamol versus oral paracetamol (95% CI)
	(2 studies)	VERY LOW1,4 due to risk of bias, inconsistency	5.6 (1.55 to 20.3)	1 per 100	3 more per 100 (from 0 more to 12 more)
Vomiting	214 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 7.25 (0.14 to 365.61)	Moderate	
				0 per 100	Not estimable

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

See appendices for full GRADE tables.

Table 4: Outcomes not suitable for GRADE analysis: IV paracetamol versus oral paracetamol for acute post-operative pain

Outcome	Study (no. of participants)	Risk of bias	Oral paracetamol (control) results	IV paracetamol (intervention) results	*P* value
Time to maximum pain relief (minutes)	Moller 2005[151] (150)	Very High	Oral acetaminophen (1g) Median (range): 1.00 (0.73,1.00)	Propacetamol bolus (2g) Median (range): 0.25 (0.25,0.27)	<0.017
				Propacetamol infusion Median (range): 0.25 (0.25,0.48)	

Outcome	Study (no. of participants)	Risk of bias	Oral paracetamol (control) results	IV paracetamol (intervention) results	*P* value
Time to rescue medication (minutes)	Fenlon 2013[65] (130)	Very High	Median: PO: 54.3 min (95% CI: 51.2, 57.4)	Median: IV: 57.2 min (95% CI:55.4, 59.2)	0.066
	Jarde 1997[98] (214)	High	People with paracetamol (oral) remedicated earlier than did those treated with propacetamol (IV). This difference was significant for the 3 and 6 hour periods		<0.05

1.4 Economic evidence

1.4.1 Included studies

No health economic studies were included.

1.4.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendices.

1.4.3 Unit costs

The average daily costs of paracetamol are provided in Table 5 to help aid consideration of cost effectiveness. A breakdown of these costs is provided in the appendices for the pain evidence review.

Table 5: Average daily costs of paracetamol

Analgesic	Average daily cost per person
Oral paracetamol	£0.04
Intravenous paracetamol	£5.02[(a)]

Source: Electronic market information tool (eMIT), Accessed September 2019[43]

(a) Cost includes disposable costs, see the appendices for the pain evidence review for a breakdown of these costs.

1.5 Evidence statements

1.5.1 Clinical evidence statements

IV paracetamol versus oral paracetamol

No outcomes were reported for health related quality of life, or any of the important outcomes.

Pain scores

Three studies showed no clinically important difference between IV paracetamol and oral paracetamol for pain up to six hours postoperatively(3 studies, n = 363, low quality evidence).

One study showed no clinically important difference between IV paracetamol and oral paracetamol in pain scores under four at twenty four hours postoperatively (1 study, n = 67, low quality of evidence)

One study showed no clinically important difference between IV paracetamol and oral paracetamol in mean pain scores at twenty four hours (1 study, n = 120, very low quality of evidence)

One study showed no clinically important difference between IV paracetamol and oral paracetamol in pain intensity up to six hours (1 study, n=214, very low quality of evidence)

One study showed no clinically important difference between IV paracetamol and oral paracetamol in pain intensity at twenty four hours postoperatively (1 study, n=67, low quality of evidence)

One study found no clinically important difference in pain relief at 1 hour postoperatively between IV paracetamol and oral paracetamol (1 study, n=128, very low quality evidence).

Rescue medication

One study showed a clinically important benefit with IV paracetamol in the number of people requesting rescue medication compared to oral paracetamol (1 study, n=128, low quality evidence).

One study found a clinically important difference with IV paracetamol for the total opioate consumption compared to oral paracetamol (1 study, n=67, low quality of evidence)

One study showed no clinically important difference between IV paracetamol and oral paracetamol in opiate consumption at up to 6 hours postoperatively (1 study, n=235, low quality evidence).

One study showed no clinically important difference between IV paracetamol and oral paracetamol in opiate consumption at 6 to 24 hours postoperatively (1 study, n=235, low quality evidence).

Adverse events

One study showed no clinically important difference in the number of people with adverse events between IV paracetamol (infusion paracetamol) and oral paracetamol (1 study, n=100, low quality of evidence)

One study showed a clinically important harm with IV paracetamol (bolus) for number of participants with adverse events compared to oral paracetamol (1 study, n=100, low quality of evidence)

One study showed no clinically important between IV paracetamol and oral paracetamol for cases of nausea (1 study, n=100, low quality evidence)

One study showed no clinically important difference in cases of nausea between IV paracetamol and oral paracetamol (1 studies, n=314, very low quality evidence)

One study showed no clinically important difference in cases of vomiting when comparing IV paracetamol and oral paracetamol (n=214, very low quality evidence)

Outcomes not suitable for GRADE anaylsis

One study showed a statistically significant benefit with IV paracetamol compared to oral paracetamol for the time taken to maximum pain relief (1 study, n=150, high quality of evidence)

One study showed no statistically significant difference between IV paracetamol and oral paracetamol for time to rescue medication (1 study, n=130, high quality of evidence)

One study showed a statistically signigicant benefit with IV paracetamol for time to rescue medication compared to oral paracetamol (1 study, n =214, high quality of evidence)

1.5.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.6 Review question 2: What is the clinical and cost effectiveness of IV paracetamol given intraoperatively in managing acute post-operative pain?

1.7 PICO table

For full details see the review protocol in appendices.

Table 6: PICO characteristics of review question

Population	Adults 18 years and over having major surgery.
Intervention	IV paracetamol and IV opioids
Comparison	IV opioids (and placebo)

Outcomes	CRITICAL:
	• health-related quality of life
	• pain reduction
	  ○ ≤ 6 hours post op
	  ○ > 6 to 24 hours post op
	• amount of additional medication use
	  ○ ≤ 6 hours post op
	  ○ > 6 to 24 hours post op
	• adverse events (including respiratory depression, nausea, vomiting, sedation)
	IMPORTANT:
	• psychological distress and mental well-being
	• symptom scores
	• functional measures
	• length of stay in intensive care
	• length of stay in hospital
	• hospital readmission

Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

1.8 Clinical evidence

1.8.1 Included studies

Three randomised controlled trials were included in the review[38, 141, 224] these are summarised in Table 7 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 8).

See appendices for the study selection flow chart, study evidence tables, forest plots and GRADE tables.

1.8.2 Excluded studies

See the excluded studies list in appendices.

1.8.3 Summary of clinical studies included in the evidence review

Table 7: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Choudhuri 2011[38]	**IV paracetamol and IV opioids:** IV paracetamol plus fentanyl 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 mg) just before induction. N=40 **IV opioids:** Fentanyl 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. N=40	Patients aged 18–70 year scheduled for laparoscopic cholecystectomy, and classified as ASA physical status I or II were included. Mean age (SD): Paracetamol and fentanyl group - 56 (16.5) Fentanyl group - 54 (19.1) India	• Pain scores (VAS) 6 hours post-operatively • Pain scores (VAS) 24 hours post-operatively • Length of hospital stay	VAS visual analogue scale
Memis 2010[141]	**IV paracetamol and IV opioids:** IV paracetamol plus meperidine N=20	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.	• Pain (BPS) at extubation • Pain (VAS) at 24 hours after surgery	BPS – behavioural pain scale VAS visual

Study	Intervention and comparison	Population	Outcomes	Comments
	IV opioids: Patients received 100 mL of serum saline IV every 6 hours and IV meperidine (Aldolan, 100 mg/2 mL) N=20	Mean age (SD): Paracetamol and Meredipine – 59.8 (12.9) Meredipine group – 60 (9.5) Turkey	• Adverse events at 24 hours postoperatively • Length of stay at ICU	analog scale
Takeda 2019[224]	**IV paracetamol and IV opioids** IV paracetamol plus fentanyl Patients received both 1000mg of IV acetaminophen every 6 hours for 24 hours after surgery and the hospitals standard post op pain control (pre op femoral nerve block and post op IV-PCA fentanyal citrate N=45 Fentanyl Patients received pre op femoral nerve block and received IC-PCA fentanyl citrate. N=52 Both groups received oral acetaminophen 1000mg 3 x per day from 24 hours to 2 weeks post op.	97 patients undergoing unilateral primary total hip arthroplasty ASA grade I-III with an ability to cooperate and understand the pain scale. Mean age (SD): Paracetamol and fentanyl group – 65.6 (11.2) Fentanyl group – 63.4 (12.2) Japan	• Pain at rest 24 hours post-surgery (NRS) • Total volume of opioid consumption during the intraoperative period and 24 hours post op • Adverse events such as nausea and vomiting	Numerical rating scale

See appendices for full evidence tables.

1.8.4 Quality assessment of clinical studies included in the evidence review

Table 8: Clinical evidence summary: IV paracetamol and IV opioid compared to IV opioid

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Iv Opioid	Risk difference with Iv Paracetamol + iv Opioid (95% CI)
Pain (BPS) at extubation	40 (1 study)	⨁⨁⊖⊖ LOW1 due to imprecision		The mean pain (bps) at extubation in the control groups was 3.6	The mean pain (bps) at extubation in the intervention groups was 1.1 lower (1.73 to 0.47 lower)
Pain (VAS) at 6h	80 (1 study) 6 hours post operation	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain (vas) at 6h in the control groups was 2.8	The mean pain (vas) at 6h in the intervention groups was 0.4 lower (0.61 to 0.19 lower)
Pain (VAS) at 24 h	217 (3 studies) 24 hours	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain (vas) at 24h in the control groups was 3.09 VAS	The mean pain (vas) at 24 h in the intervention groups was 0.08 lower (0.26 lower to 0.1 higher)
Amount of additional medication (Meperidine) 24 h post-surgery	40 (1 study) 24 hours	⨁⨁⊖⊖ LOW1 due to imprecision		The mean additional medication at 24h in the control groups was 198mg	The mean amount of additional medication (meperidine) 24 h post-surgery in the intervention groups was 121.25mg lower (151.42 to 91.08 lower)
Total opioid consumption (morphine	97	⨁⨁⨁⊖		The mean total	The mean total opioid consumption in the

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Iv Opioid	Risk difference with Iv Paracetamol + iv Opioid (95% CI)
equivalents) 24 h post-surgery	(1 study)	MODERATE1 due to imprecision		opioid consumption in the control groups was 57.83 mg	intervention groups was 5.76 lower (9.81 to 1.71 lower)
Adverse events	133 (2 studies) 24 hours	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 0.26 (0.08 to 0.87)	Moderate	
				176 per 1000	130 fewer per 1000 (from 26 fewer to 162 fewer)
Length of stay at ICU (hours)	120 (1 study)	⊕⊕⊕⊖ MODERATE1 due to imprecision		The mean length of stay at icu in the control groups was 27	The mean length of stay at ICU in the intervention groups was 1 lower (3.19 lower to 1.19 higher)
Length of hospital stay (days)	80 (1 study)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean length of hospital stay in the control groups was 1.2	The mean length of hospital stay in the intervention groups was 0.1 higher (0.19 lower to 0.39 higher)

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 is from studies at very high risk of bias.
3 Downgraded due to heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 9: Evidence not suitable for GRADE analysis: IV paracetamol and IV opioid compared to IV opioid

Outcome	Study (no. of participants)	Risk of bias	Comparison results	Intervention results	*P* value
Number of patients requiring rescue analgesic in post-operative period	Chaudhuri 2011(80)	High	Proportion 14/40	Proportion 13/40	<0.05

See appendices for full GRADE tables.

1.9 Economic evidence

1.9.1 Included studies

No health economic studies were included.

1.9.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendices.

1.9.3 Unit costs

The average daily costs of intravenous opioids and paracetamol are provided in Table 10 to help aid consideration of cost effectiveness. A breakdown of these costs is provided in the appendices for the pain evidence review.

Table 10: Average daily costs of intravenous opioid and intravenous paracetamol

Analgesic	Average daily cost per person (range)[(a)]
Intravenous opioid	£4.92 (£3.77 – £6.07)
Intravenous opioid & paracetamol	£6.71 (£4.66 - £7.86)
Patient controlled analgesia (opioid)	£21.10 (£16.36 - £23.79)
Patient controlled analgesia (opioid) & paracetamol	£22.89 (£17.25 - £25.58)

Sources: British National Formulary, Accessed September 2019[101]; Electronic market information tool (eMIT), Accessed September 2019[43]

(a) Costs include disposable costs, see the appendices for the pain evidence review for a breakdown of these costs.

1.10 Evidence statements

1.10.1 Clinical evidence statements

IV paracetamol plus IV opioid versus IV opioid

No outcomes were reported for health related quality of life or the following important outcomes; psychological distress and mental well-being, symptom scores, functional measures and hospital readmission.

Pain relief

One study showed a clinically important benefit with IV paracetamol and IV opioid in pain at extubation compared to IV opioid alone (1 study, n=40, low quality)

One study showed no clinically important difference in pain six hours postoperatively between IV paracetamol and IV opioid and IV opioid alone (1 study, n=80, very low quality)

Three studies found no clinically important differnece in pain twenty hours postoperatively between IV paracetamol and IV opioid and IV opioid alone (1 study, n=217, very low quality)

Rescue medication

One study showed a clinically important benefit with IV paracetamol and IV opioid in the amount of additional meperidine used twenty four hours postoperatively compared to IV opioid alone (1 study, n=40, low quality)

One study found a clinically important benefit with IV paracetamol and IV opioid in the total amount of opioid given compared to IV opioid twenty four hours post-surgery (1 study, n=97, moderate quality evidence)

Adverse events

Two studies showed a clinically important benefit with IV paracetamol and IV opioids in the reduction of adverse events twenty four hours postoperatively compared to IV opioid alone (2 studies, n=133, moderate quality)

Length of stay

One study found no clinically important difference in the length of stay in ICU (hours) postoperatively between IV paracetamol and IV opioid and IV opioid alone (1 study, n=120, moderate quality)

One study found no clinically important difference in the length of stay in hospital (days) postoperatively between IV paracetamol and IV opioid compared to IV opioid alone (1 study, n=80, low quality)

1.10.2 Health economic evidence statements

- No relevant economic evaluations were identified.

2 Simple anlagesics: Non-steroidal anti-inflammatory drugs (NSAIDs)

2.1 Methods approach

This section of the report addresses the clinical and cost effectiveness of NSAIDs in the 24 hour post operative period. The first clinical review evaluates the effectiveness of NSAIDs and then the second review examines which of the NSAIDs is the most clinically and cost effective. The effectiveness of NSAIDs in the immediate post operative period has been extensively researched. A preliminary search idenitifed over 900 trial publications including 11 Cochrane systematic reviews and 2 overviews of Cochrane reviews. A more recent NMA[156] performed by the authors of the overviews of Cochrane reviews and communication with the lead author has indicated thatevidence in this area has stabilised, suggesting that updated searches of the evidence have not identified any trials that would add further to this evidence base. A Cohrane statement has outlined that no updates of the included reviews are expected in the next 5 years with no new data likely to be available that change the conclusions for at least 10 years. The Cocrhane overview will subsequently be reassessed for updating in 2027.

As such, the first review here evaluates and summarises these Cochrane reviews. Evidence on the individual single dose NSAIDs and Cox-2 inhibitors from two overviews of Cochrane reviews[154, 155] reporting pain management and adverse events were extracted. The overviews of Cochrane reviews do not report an overall summary effect of NSAIDs compared to placebo. We have combined the data from the separate Cochrane reviews to give an overall effect of the NSAIDs for each outcome. This method was repeated for the Cox-2 inhibitors.The Cochrane reviews included in these overviews and those identified from our literature search were also cross-checked for further relevant outcome data. Data on rescue medication use was subsequently extracted from these Cochrane reviews. The reviews were assessed for risk of bias using the ROBIS checklist.

The approach to examine which of the NSAIDs is the most clinically and cost effective is described in the POC Methods report in the sections explaining the review of intervention studies.

2.2 Review question 1: What is the clinical and cost effectiveness of NSAIDs for managing acute postoperative pain?

2.3 PICO table

For full details see the review protocol in appendices.

Table 11: PICO characteristics of review question

Population	Adults (18 years and older) who have undergone surgery.
Interventions	• non-steroidal anti-inflammatory drugs by any route, including : ○ indomethacin ○ ibuprofen ○ diclofenac ○ naproxen ○ ketorolac,

	• COX2- inhibitor (for example, celecoxib)
Comparisons	• placebo •

Outcomes	CRITICAL:
	• health-related quality of life
	• pain reduction
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• amount of additional medication use
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications)
	IMPORTANT:
	• psychological distress and mental well-being
	• symptom scores
	• functional measures
	• length of stay in intensive care
	• length of stay in hospital
	• hospital readmission

Study design	Systematic reviews of randomised controlled trials.

2.4 Clinical evidence

2.4.1 Included studies

Two overview of Cochrane reviews[154, 155] and 11 Cochrane reviews[42, 51-54, 74, 150, 197, 219, 230, 243] were included in the review; these are summarised in Table 12 and Table **13** below. Evidence from these studies is summarised in the clinical evidence summary below.

NSAIDs

Overall summary effect of NSAIDs by outcome.

- Table 14: Clinical evidence summary: NSAIDs versus placebo. (see fores plots in separate appendices document)

Summaries of the individual NSAIDs and different dosages by outcome.

- Table 15: Evidence summary from Moore et al[155]: Individual NSAIDs versus placebo. Pain relief
- Table 16: Evidence summary from Moore et al [154]: Individual NSAIDs versus placebo. Adverse events
- Table 17: Evidence summaries from the individual Cochrane reviews: NSAIDs versus placebo rescue medication

COX-2 inhibitors

Overall summary effect of COX-2 inhibitors by outcomes

- Table 18: Clinical evidence summary: COX-2 inhibitors versus placebo.

Summaries of the individual COX-2 inhibitors and different dosages by outcome

- Table 19: Evidence summary from Moore et al [155]: Individual cox-2 inhibitor versus placebo. Pain relief

- Table 20: Evidence summary from Moore et al[154]: Individual cox-2 inhibitor versus placebo. Adverse event

- Table 21: Evidence summaries from the of individual Cochrane reviews: Individual cox-2 inhibitor versus placebo. Rescue medication.

2.4.2 See appendices for the study selection flow chart, study evidence tables, forest plots and GRADE tables. Excluded studies

See the excluded studies list in the appendices.

2.4.3 Summary of the Cochrane reviews included in the evidence review

Table 12: Summary of the overview of Cochrane reviews

Overview of Cochrane reviews	Intervention and comparison	Population	Outcomes	Comments
Moore 2015 (efficacy)[154]	Thirty-nine Cochrane reviews of randomised trials have examined the analgesic efficacy of individual drug interventions in acute postoperative pain. The Cochrane reviews included adult participants with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery. This overview brings together the results of those individual reviews and assesses the reliability of available data.		• Pain	Results from NSAIDs versus placebo and cox-2 inhibitors versus placebo extracted.
Moore 2015 (adverse events)[155]	Thirty-nine Cochrane reviews of randomised trials have examined the adverse events associated with individual drug interventions in acute postoperative pain. The Cochrane reviews included adult participants with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery. This overview brings together the results of those individual reviews.		• Adverse events • Serious adverse events • Mortality	Results from NSAIDs versus placebo and cox-2 inhibitors versus placebo extracted.

Table 13: Summary of the Cochrane reviews included in the evidence review

Cochrane review	Intervention and comparison	Population	Outcomes	Comments
Derry 2012[52]	Aspirin versus placebo	Adult participants (>15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery.	• Rescue analgesia	Cochrane review
Gaskell 2017[74]	Dexketoprofen versus placebo Ketoprofen versus placebo			
Derry 2015[54]	Diclofenac versus placebo			
Wasey 2010[243]	Diflunisal versus placebo			
Tirunagari 2009[230]	Etodolac versus placebo			

Cochrane review	Intervention and comparison	Population	Outcomes	Comments
Sultan 2009[219]	Flurbiprofen versus placebo			
Derry 2009[51]	Ibuprofen versus placebo			
Moll 2011[150]	Mefenamic acid versus placebo			
Derry 2013[53]	Celecoxib versus placebo			
Clarke 2012[42]	Etoricoxib versus placebo			
Roy 2010[197]	Lumiracoxib versus placebo			

See appendices for full evidence tables.

2.4.4 Quality assessment of the Cochrane reviews included in the evidence review

Table 14: Clinical evidence summary: NSAIDs versus placebo.

Outcomes	No of Participants	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with NSAIDs (95% CI)
Participants with at least 50% pain relief over 6 hours	29191	⊕⊕⊕⊖ MODERATE1 due to inconsistency	RR 3.17 (3.04 to 3.30)	Moderate	
				155 per 1000	336 more per 1000 (from 316 more to 356 more)
Participants with at least one adverse event	20846	⊕⊕⊕⊕ HIGH	RR 1.07 (1.00 to 1.14)	Moderate	
				137 per 1000	10 more per 1000 (from 0 more to 19 more)
Participants using rescue	14010	⊕⊕⊖⊖	RR 0.6	Moderate	

Outcomes	No of Participants	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with NSAIDs (95% CI)
medication at 6 hours		LOW1 due to inconsistency	(0.58 to 0.62)	725 per 1000	290 fewer per 1000 (from 275 fewer to 305 fewer)

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

Table 15: Evidence summary from Moore et al[155]: Individual NSAIDs versus placebo. Pain relief

Drug	Dose (mg)	Studies	Participants	At least 50% maximum pain relief over 4 - 6 hours				Susceptibility to publication bias
				Number with outcome/total		Risk ratio (95% CI)	NNT (95% CI)	
				Active	placebo			
Aspirin	600/650	65	4965	983/2496	379/2469	2.5 (2.3 to 2.8)	4.2 (3.8 to 4.6)	6856
Aspirin	1000	6	618	138/340	40/278	2.7 (2.0 to 3.7)	4.2 (3.8 to 4.6)	853
Aspirin	1200	3	249	85/140	25/109	3.3 (1.8 to 6.3)	2.4 (1.9 to 3.2)	789
Dexketoprofen	10/12.5	5	452	104/230	38/222	2.7 (2.0 to 3.7)	3.6 (2.8 to 5.0)	804
Dexketoprofen	20/25	6	523	129/225	38/248	3.3 (2.4 to 4.5)	3.2 (2.6 to 4.1)	1111
Diclofenac fast-acting	25	2	325	36/165	4/160	8.7 (3.2 to 24)	5.2 (3.8 to 8.0)	325
Diclofenac fast-acting	50	4	486	156/214	46/232	2.9 (3.2 to 3.8)	2.4 (2.0 to 3.0)	1539
Diclofenac potassium	25	4	502	140/248	37/274	3.9 (2.8 to 5.3)	2.4 (2.0 to 2.9)	1590

Drug	Dose (mg)	Studies	Participants	At least 50% maximum pain relief over 4 - 6 hours				Susceptibility to publication bias
				Number with outcome/total		Risk ratio (95% CI)	NNT (95% CI)	
				Active	placebo			
Diclofenac potassium	50	7	757	253/398	60/359	3.7 (2.9 to 4.7)	2.1 (1.9 to 2.5)	2848
Diclofenac potassium	100	6	589	196/300	39/289	4.8 (3.6 to 6.5)	1.9 (1.7 to 2.3)	2511
Diclofenac sodium	50	2	313	58/193	18/120	2.0 (1.3 to 3.3)	6.6 (4.1 to 17)	161
Diflunisal	250	3	195	49/98	16/97	2.9 (1.8 to 4.6)	3.3 (2.3 to 5.5)	396
Diflunisal	500	6	391	104/198	27/193	3.8 (2.6 to 5.4)	2.6 (2.1 to 3.3)	1113
Diflunisal	1000	5	357	112/182	26/175	4.1 (2.9 to 6.0)	2.1 (1.8 to 2.6)	1343
Etodolac	50	4	360	44/154	34/206	1.7 (1.1 to 2.6)	8.3 (4.8 to 30)	74
Etodolac	100	5	498	103/251	50/247	2.0 (1.5 to 2.7)	4.8 (3.5 to 7.8)	540
Etodolac	200	7	670	145/333	44/337	3.3 (2.5 to 4.5)	3.3 (2.7 to 4.2)	1360
Etodolac	400	3	222	52/134	4/88	9.0 (3.4 to 24)	2.9 (2.3 to 4.0)	544
Fenoprofen	200	4	287	83/146	19/141	4.2 (2.7 to 6.4)	2.3 (1.9 to 3.0)	961
Flurbiprofen	25	3	208	36/102	5/106	7.0 (2.9 to 16)	3.3 (2.5 to 4.9)	422
Flurbiprofen	50	10	692	245/353	108/339	2.2 (1.9 to 2.6)	2.7 (2.3 to 3.3)	1871
Flurbiprofen	100	7	416	139/215	48/201	2.8 (2.2 to 3.6)	2.5 (2.0 to 3.1)	1248

Drug	Dose (mg)	Studies	Participants	At least 50% maximum pain relief over 4 - 6 hours				Susceptibility to publication bias
				Number with outcome/total		Risk ratio (95% CI)	NNT (95% CI)	
				Active	placebo			
Ibuprofen	50	3	316	50/159	16/157	3.2 (1.9 to 5.1)	4.7 (3.3 to 8.0)	356
Ibuprofen	100	4	396	60/192	16/204	3.7 (2.3 to 5.9)	4.3 (3.2 to 6.4)	525
Ibuprofen	200	18	2103	448/1094	67/1009	6.5 (5.1 to 8.2)	2.9 (2.7 to 3.2)	5149
Ibuprofen	400	51	5604	1596/3070	289/2543	4.6 (4.0 to 5.1)	2.5 (2.4 to 2.6)	16,812
Ibuprofen	600	3	203	88/114	36/89	2.0 (1.5 to 2.6)	2.7 (2.0 to 4.2)	549
Ibuprofen (fast acting)	200	7	828	270/478	34/350	5.7 (4.2 to 7.9)	2.1 (1.9 to 2.4)	3115
Ibuprofen (fast acting)	400	13	1364	427/658	85/466	3.9 (3.2 to 4.7)	2.1 (1.9 to 2.3)	5131
Ketoprofen	12.5	3	274	77/138	18/136	4.2 (2.7 to 6.6)	2.4 (1.9 to 3.1)	868
Ketoprofen	25	8	535	175/281	31/254	4.9 (3.5 to 6.9)	2.0 (1.8 to 2.3)	2140
Ketoprofen	50	8	624	151/314	56/310	2.7 (2.0 to 3.5)	3.3 (2.7 to 4.3)	1267
Ketoprofen	100	5	321	106/161	28/160	3.6 (2.5 to 5.1)	2.1 (1.7 to 2.6)	1208
Lornoxicam	8	3	273	71/155	13/118	4.7 (2.7 to 8.1)	2.9 (2.3 to 4.0)	668
Mefenamic acid	500	2	256	60/126	29/130	2.1 (1.5 to 3.1)	4.0 (2.7 to 7.1)	384

Drug	Dose (mg)	Studies	Participants	At least 50% maximum pain relief over 4 - 6 hours				Susceptibility to publication bias
				Number with outcome/total		Risk ratio (95% CI)	NNT (95% CI)	
				Active	placebo			
Naproxen	200/220	2	202	54/120	13/82	2.9 (1.6 to 5.1)	3.4 (2.4 to 5.8)	392
Naproxen	400/440	3	334	103/210	14/124	4.8 (2.8 to 8.4)	2.7 (2.2 to 3.5)	903
Naproxen	500/550	9	784	200/394	59/390	3.4 (2.6 to 4.4)	2.7 (2.3 to 3.3)	2120
Piroxicam	20	3	280	89/141	36/139	2.5 (1.8 to 3.3)	2.7 (2.1 to 3.8)	757

Moore RA, Derry S, Aldington D, Wiffen PJ, Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews, Issue 9. 2015. Copyright Cochrane Collaboration, reproduced with permission.

Table 16: Evidence summary from Moore et al [154]: Individual NSAIDs versus placebo. Adverse events

Drug	Dose (mg)	Studies	Participants	Participants with at least one adverse event		
				Per cent with outcome		Risk ratio (95% CI)
				Active	placebo	
Aspirin	600/650	46	3633	11	9.5	1.2 (1.0 to 1.4)
Aspirin	900/1000	4	404	26	12	1.6 (1.1 to 2.3)*
Dexketoprofen	10/12.5	3	258	9	46	0.6 (0.3 to 1.3)
Dexketoprofen	20/25	5	413	20	46	1.3 (0.8 to 2.1)
Diclofenac fast-acting	All doses	5	636	8	46	1.0 (0.6 to 1.8
Diclofenac	All doses	7	1090	8	46	1.0 (0.7 to 1.6)

Drug	Dose (mg)	Studies	Participants	Participants with at least one adverse event		
				Per cent with outcome		Risk ratio (95% CI)
				Active	placebo	
potassium						
Diflunisal	250	3	195	3	6	0.5 (0.2 to 1.8)
Diflunisal	500	7	462	18	15	1.3 (0.8 to 1.9)
Diflunisal	1000	6	417	29	16	1.8 (1.2 to 2.6)*
Etodolac	50	4	320	8	6	1.4 (0.6 to 3.2)
Etodolac	100	5	459	11	7	1.6 (0.9 to 2.8)
Etodolac	200	7	633	22	17	1.2 (0.9 to 1.7)
Etodolac	400	4	310	28	34	0.8 (0.5 to 1.2)
Fenoprofen	200	4	287	6	6	0.9 (0.4 to 2.1)
Flurbiprofen	25	3	221	14	16	0.9 (0.5 to 1.7)
Flurbiprofen	50	8	564	13	17	0.8 (0.5 to 1.1)
Flurbiprofen	100	5	342	12	12	1.0 (0.6 to 1.8)
Ibuprofen	50	2	225	10	7	1.3 (0.6 to 3.0)
Ibuprofen	100	3	310	14	13	1.2 (0.7 to 2.1)

Drug	Dose (mg)	Studies	Participants	Participants with at least one adverse event		
				Per cent with outcome		Risk ratio (95% CI)
				Active	placebo	
Ibuprofen	200	14	1808	19	19	0.9 (0.7 to 1.02)
Ibuprofen	400	40	4867	17	16	0.9 (0.8 to 1.04)
Ketoprofen	12.5	3	274	6	4	1.3 (0.5 to 3.6)
Ketoprofen	25	7	490	10	10	1.2 (0.7 to 2.0)
Ketoprofen	50	4	278	21	14	1.6 (0.9 to 2.6)
Ketoprofen	100	3	175	22	18	1.2 (0.7 to 2.2)
Lornoxicam	8	3	273	44	23	1.4 (0.9 to 2.2)
Mefenamic acid	500	2	104	13	6	2.2 (0.7 to 7.2)
Naproxen	400/440	3	334	22	17	1.3 (0.8 to 2.2)
Naproxen	500/550	9	784	27	29	1.0 (0.7 to 1.2)
Serious adverse events were rare, occurring a rate of about 1 in 3200 people. In total, serious adverse events in studies involving NSAIDs and cox-2 inhibitors were reported for 10 participants: three taking ibuprofen; one taking etodolac; one taking naproxen and three taking placebo. No deaths were reported						
* indicates statistically significant risk ratio						

Moore RA, Derry S, Aldington D, Wiffen PJ, Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews, Issue 9. 2015. Copyright Cochrane Collaboration, reproduced with permission.

Table 17: Evidence summaries from the individual Cochrane reviews: NSAIDs versus placebo rescue medication

Drug	Dose (mg)	Studies	Participants	Participants using rescue medication at 6 hours		
				Number with outcome		Risk ratio (95% CI)
				Active	placebo	
Aspirin[1]	600/650	20	1923	530/955	696/968	0.77 (0.73 to 0.82)
Aspirin[1]	900/1000	2	233	78/116	97/117	0.82 (0.73 to 0.95)
Dexketoprofen[2]	10/12.5	5	480	107/243	153/237	0.68 (0.58 to 0.81)
Dexketoprofen[2]	20/25	7	635	159/331	209/304	0.68 (0.59 to 0.77)
Diclofenac fast-acting[3]	50	4	486	83/254	164/232	0.46 (0.38 to 0.56)
Diclofenac fast-acting[3]	100	2	168	46/92	59/76	0.61 (0.48 to 0.77)
Diclofenac Potassium[3]	25	4	502	127/248	181/254	0.72 (0.63 to 0.82)
Diclofenac Potassium[3]	50	7	757	144/398	248/359	0.52 (0.45 to 0.60)
Diclofenac Potassium[3]	100	6	589	102/300	208/289	0.45 (0.38 to 0.54)
Diclofenac sodium[3]	50	2	284	103/175	75/109	0.82 (0.69 to 0.98)
Diflunisal[4]	500	6	390	54/197	128/193	0.41 (0.33 to 0.52)

Drug	Dose (mg)	Studies	Participants	Participants using rescue medication at 6 hours		
				Number with outcome		Risk ratio (95% CI)
				Active	placebo	
Diflunisal[4]	1000	6	409	48/206	153/203	0.31 (0.24 to 0.40)
Etodolac[5]	100	2	121	13/60	24/61	0.56 (0.32 to 0.96)
Etodolac[5]	200	3	219	67/110	84/109	0.79 (0.66 to 0.94)
Etodolac[5]	400	3	191	67/106	64/85	0.86 (0.72 to 1.04)
Etodolac[5]	1200	1	95	18/48	40/47	0.44 (0.30 to 0.65)
Flurbiprofen[6]	50	6	425	53/212	140/213	0.38 (0.30 to 0.48)
Flurbiprofen[6]	100	4	239	20/122	79/117	0.24 (0.16 to 0.36)
Ibuprofen[7]	50	2	208	30/102	53/106	0.61 (0.44 to 0.84)
Ibuprofen[7]	100	3	296	54/143	88/153	0.69 (0.57 to 0.84)
Ibuprofen[7]	200	9	794	215/452	259/342	0.63 (0.57 to 0.70)
Ibuprofen[7]	400	31	2983	737/1756	975/1227	0.54 (0.51 to 0.57)
Ketoprofen[2]	12.5	2	198	79/99	97/99	0.81 (0.74 to 0.90)
Ketoprofen[2]	25	6	402	99/216	147/186	0.60 (0.52 to 0.69)
Ketoprofen[2]	50	6	468	93/236	162/232	0.56 (0.47 to 0.66)

Drug	Dose (mg)	Studies	Participants	Participants using rescue medication at 6 hours		
				Number with outcome		Risk ratio (95% CI)
				Active	placebo	
Ketoprofen[2]	80-100	4	259	57/130	104/129	0.54 (0.44 to 0.67)
Mefenamic acid [8]	500	2	256	59/126	81/130	0.75 (0.61 to 0.93)

1.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.

2. 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.

3. Derry S, Wiffen PJ, Moore RA. Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2015, Issue 7. Copyright Cochrane Collaboration, reproduced with permission.

4. Wasey JO, Derry S, Moore RA, McQuay HJ. Single dose oral diflunisal for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2010, Issue 4. Copyright Cochrane Collaboration, reproduced with permission.

5.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. Copyright Cochrane Collaboration, reproduced with permission.

6. Sultan A, McQuay HJ, Moore RA, Derry S. Single dose oral flurbiprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2008, Issue 4. Copyright Cochrane Collaboration, reproduced with permission.

7.Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database Systematic Reviews 2009, Issue 3. Copyright Cochrane Collaboration, reproduced with permission.

8. 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.

Table 18: Clinical evidence summary: COX-2 inhibitors versus placebo.

Outcomes	No of Participants	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with COX-2 inhibitors (95% CI)
Participants with at least 50% pain relief over 6 hours	2805	⊕⊕⊖⊖ LOW1 due to inconsistency	RR 5.74 (4.66 to 7.07)	Moderate	
				91 per 1000	431 more per 1000 (from 333 more to 552 more)

Outcomes	No of Participants	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with COX-2 inhibitors (95% CI)
Participants with at least one adverse event	2913	⊕⊕⊕⊕ HIGH	RR 0.92 (0.82 to 1.04)	Moderate	
				311 per 1000	25 fewer per 1000 (from 56 fewer to 12 more)
Participants using rescue medication at 6 hours	1722	⊕⊕⊖⊖ LOW1 due to inconsistency	RR 0.73 (0.69 to 0.76)	Moderate	
				909 per 1000	245 fewer per 1000 (from 218 fewer to 282 fewer)
1 Downgraded by because the point estimate varies widely across studies, I2=50%, p=0.04.					

Table 19: Evidence summary from Moore et al [155]: Individual cox-2 inhibitor versus placebo. Pain relief

Drug	Dose (mg)	Studies	(participants)	At least 50% maximum pain relief over 4 - 6 hours				Susceptibility to publication bias
				Number with outcome/total		Risk ratio (95% CI)	NNT (95% CI)	
				Active	placebo			
Celecoxib	200	4	705	149/423	32/282	3.5 (2.4 to 5.1)	4.2 (3.4 to 5.6)	974
Celecoxib	400	5	722	202/466	12/256	10 (5.7 to 8)	2.6 (2.3 to 3.0)	2055
Etoricoxib	120	6	798	332/503	34/295	5.6 (4.0 to 7.8)	1.8 (1.7 to 2.0)	3635
Etoricoxib	180/240	2	199	129/150	6/49	6.4 (3.1 to 14)	1.5 (1.3 to 1.7)	1128
Lumiracoxib	400	4	578	183/366	17/212	6.9 (4.1 to 11)	2.4 (2.1 to 2.8)	1830

Moore RA, Derry S, Aldington D, Wiffen PJ, Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews, Issue 9. 2015. Copyright Cochrane Collaboration, reproduced with permission.

Table 20: Evidence summary from Moore et al[154]: Individual cox-2 inhibitor versus placebo. Adverse event

Drug	Dose (mg)	Studies	(participants)	Participants with at least one adverse event		
				Per cent with outcome		Risk ratio
				Active	placebo	(95% CI)
Celecoxib	200	4	669	16	17	0.9 (0.6 to 1.3)
Celecoxib	400	6	725	34	46	1.0 (0.8 to 1.2)
Etoricoxib	120/180/240	5	1029	32	38	0.9 (0.7 to 1.1)
Lumiracoxib	400	3	460	13	18	0.7 (0.4 to 1.3)
Serious adverse events were rare, occurring a rate of about 1 in 3200 people. In total, serious adverse events in studies involving NSAIDs and cox-2 inhibitors were reported for 10 participants: two taking rofecoxib and three taking placebo. No deaths were reported						

Moore RA, Derry S, Aldington D, Wiffen PJ, Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews, Issue 9. 2015. Copyright Cochrane Collaboration, reproduced with permission.

Table 21: Evidence summaries from the of individual Cochrane reviews: Individual cox-2 inhibitor versus placebo. Rescue medication.

Drug	Dose (mg)	Studies	(participants)	Participants requiring rescue medication over 24 hours		
				Per cent with outcome		Risk ratio
				Active	placebo	(95% CI)
Celecoxib[1]	200	2	271	113/181	85/90	0.78 (0.70 to 0.86)
Celecoxib[1]	400	3	518	228/364	140/154	0.68 (0.62 to 0.74)
Etoricoxib[2]	120/180/240	4	505	154/306	178/199	0.74 (0.67 to 0.81)

Drug	Dose (mg)	Studies	(participants)	Participants requiring rescue medication over 24 hours		
				Per cent with outcome		Risk ratio (95% CI)
				Active	placebo	
Lumiracoxib[3]	400	3	428	169/266	147/162	0.72 (0.65 to 0.80)

1.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.

2.Clarke R, Derry S, Moore RA. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 4. Copyright Cochrane Collaboration, reproduced with permission.

3. 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.

See appendices for full GRADE tables.

2.5 Economic evidence

2.5.1 Included studies

No health economic studies were included.

2.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendices.

2.5.3 Unit costs

The average daily costs of NSAIDs and COX-2 inhibitors are provided in Table 22 **Error! Reference source not found.** to help aid consideration of cost effectiveness. A breakdown of these costs is provided in the appendices for the pain evidence review.

Table 22: Average daily costs of NSAIDs and COX-2 inhibitors

Analgesic	Average daily cost per person (range)
Oral NSAID	£0.07 (£0.04 - £0.11)
Intravenous NSAID	£4.19 (£3.66 - £4.72)[(a)]
Oral COX-2 inhibitor	£0.04
Intravenous COX-2 inhibitor	£14.57[(a)]

Sources: British National Formulary, Accessed September 2019[101]; Electronic market information tool (eMIT), Accessed September 2019[43]

(a) Costs include disposable costs, see the appendices for the pain evidence review for a breakdown of these costs.

2.6 Evidence statements

2.6.1 Clinical evidence statements

No outcomes were reported for health related quality of life, or any of the important outcomes.

NSAIDs versus placebo

Pain relief

Three hundred and twelve studies showed a clinically important benefit of NSAIDs for people achieving at least 50% maximum pain relief over 4 - 6 hours compared to placebo (312 studies, n=29191,moderate quality evidence))

Adverse events

Two hundred and nineteen studies showed no clinically important difference between NSAIDs and placebo for people experiencing at least one adverse event (219 studies, n=20846, high quality evidence)

Rescue medication

One hundred and fifty five studies showed a clinically important benefit of NSAIDs in the number of people using rescue medication at 6 hours compared to placebo (155 studies, n=14010, low quality evidence)

COX-2 inhibitors versus placebo

Pain relief

Twenty one studies showed a clinically important benefit with COX-2 inhibitors for people achieving at least 50% maximum pain relief over 4 - 6 hours compared to placebo(21 studies, n=2805, low quality evidence) **Adverse events**

Eighteen studies showed no clinically important difference between COX-2 inhibitors and placebo for people experiencing at least one adverse event (18 studies n=2913, high quality evidence)

Rescue medication

Twelve studies showed a clinically important benefit with COX-2 inhibitors in the number of people using rescue medication at 6 hours compared to placebo (12 studies, n=1722, low quality evidence)

2.6.2 Health economic evidence statements

- No relevant health economic studies were indentified.

2.7 Review question 2: Which is the most clinical and cost effective intervention within the class of NSAIDs for managing acute postoperative pain?

2.8 PICO table

For full details see the review protocol in appendices.

Table 23: PICO characteristics of review question

Population	Adults (18 years and older) who have undergone surgery.
Interventions	• non-steroidal anti-inflammatory drugs by any route, including : ○ indomethacin ○ ibuprofen ○ diclofenac ○ naproxen ○ ketorolac, • COX2- inhibitor (for example, celecoxib)
Comparisons	• To each other
Outcomes	CRITICAL: • health-related quality of life • pain reduction ○ ≤ 6 hours post op ○ > 6 hours- 24 hours post op • amount of additional medication use ○ ≤ 6 hours post op ○ > 6 hours- 24 hours post op • adverse events (including respiratory depression, nausea, vomiting, cardiac events , acute kidney injury, gastrointestinal complications, bone healing complications) IMPORTANT: • psychological distress and mental well-being • symptom scores • functional measures • length of stay in intensive care • length of stay in hospital • hospital readmission
Study design	Randomised controlled trials and systematic reviews of randomised controlled trials.

2.9 Clinical evidence

2.9.1 Included studies

Forty-one randomised controlled trials[3, 7, 9, 10, 12, 20, 22, 28, 33, 37, 39, 40, 47, 58, 67, 68, 70, 71, 96, 103, 111, 116, 128, 133, 139, 140, 153, 158, 165, 170, 186, 208, 227, 228, 235, 236, 239, 242, 244, 248, 251] were included in the review comparing different NSAIDs and COX2-inhibitors.

21 studies compared NSAIDs to other NSAIDS; 2 studies [20, 103] comparing diclofenac and ibuprofen, 2 studies [69, 111] comparing ibuprofen and naproxen, 16 studies [3, 33, 39, 40, 67, 68, 71, 96, 116, 153, 158, 170, 186, 227, 228, 242] comparing diclofenac and Ketorolac, and 1 study[239] comparing Ibuprofen and ketorolac. 20 studies compared NSAIDs to COX2 inhibitors; 9 studies [22, 28, 47, 128, 139, 140, 165, 208, 251] comparing ketorolac and parecoxib; 3 studies [12, 133, 244] comparing Celecoxib and diclofenac.,6 studies[7, 9, 10, 37, 58, 248] comparing Celecoxib and ibuprofen, and 2 studies [235, 236] comparing Celecoxib and Ketorolac, these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See appendices for the study selection flow chart, study evidence tables, forest plots and GRADE tables.

2.9.2 Excluded studies

See the excluded studies list in appendices.

2.9.3 Summary of clinical studies included in the evidence review

Table 24: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
NSAIDs compared to NSAIDs				
Ibuprofen compared to diclofenac				
Bakshi 1994[20]	**Ibuprofen:** Ibuprofen 400mg postoperatively (n=80) **Diclofenac:** Diclofenac dispersible 50mg (n=83) **Rescue analgesia:** Unclear	Patients up to the age of 65, suffering from at least severe pain after surgical extraction of an impacted lower third molar Age - Mean (range): Diclofenac: 27.7 (18-68); Ibuprofen: 26.9 (18-60). Germany	• Pain scores	
Joshi 2004[103]	**Diclofenac:** Diclofenac 100mg given preoperatively (n=29) **Ibuprofen:** Ibuprofen 600mg given 1 hour preoperatively (n=31) **Rescue analgesia:** 1g of paracetamol and codeine 30mg once in 6h (maximum 8 tablets a day)	Patients ASA I or II who were to have third molar teeth removed under general anaesthesia Age - Mean (SD): Mean age: 26 (6) United Kingdom	• Pain score	
Ibuprofen compared to naproxen				

Fricke 1993[69]	**Naproxen:** Patients were instructed to take dose of study drug for moderate pain. Patients received Naproxen Sodium 440mg (n=81) **Ibuprofen:** Patients were instructed to take dose of study drug for moderate pain. Patients received Ibuprofen 400mg (n=81) **Rescue analgesia:** Rescue medication taken but not specified	Patients aged above >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 Age - Mean (SD): Naproxen: 24.1 (6.8); Ibuprofen: 22.5 (4.5). USA	• Pain scores	
Kiersch 1993[111]	**Naproxen:** Naproxen sodium 220mg following dental surgery when patients are experiencing moderate pain after extraction (n=80) **Ibuprofen:** Ibuprofen 200mg following dental surgery when patients are experiencing moderate pain after extraction (n=81) **Rescue analgesia:** Not specified	Patients >15 years of age; experiencing at least moderate pain following extraction of one or two bony impacted third molars Age - Mean (SD): Naproxen: 25.4 (6.9); Ibuprofen; 24.9 (6.3). USA	• Pain scores	
Ibuprofen compared to ketorolac				
Uribe 2018[239]	**Ibuprofen:** Two doses of 800mg IV	Patients scheduled to undergo arthroscopic knee	• Dose of opioid ≤ 6 hours	

	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 (n=20) **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 (n=31)	surgery under general anaesthesia who were 18 years and older Age – Mean (SD): Ibuprofen: 42.32 ± 12.37; Ketorolac: 44.6 ± 13.03 USA		
Diclofenac and Ketorolac				
Aftab 2008[3]	**Ketorolac**: During the postoperative period received Ketorolac 30mg IV 8 hourly (n=30) **Diclofenac**: During the postoperative period received Diclofenac 75mg IV 12 hourly (n=30) **Rescue analgesia**: Nalbuphine 0.1mg/kg was administered to patients if pain persistently remained above two on visual analogue scale	Patients ASA physical status I and II, age ranged 45 – 50 years undergoing laparoscopic surgery Age - Mean (SD): Ketorolac: 44.17 ± 12.05; Diclofenac: 43.50 ± 12.56 Pakistan	• Opioid consumption • Adverse events	
Canadell-Carafi 1990[33]	**Ketorolac:** 10mg Ketorolac suppositories, four times a day. (n=37)	Patients aged 18 - 65 suffering moderate to severe pain following orthopaedic surgery (total hip	• Pain score	

	Diclofenac: Diclofenac 100mg suppositories, given twice a day (n=39) **Rescue analgesia:** Paracetamol 500mg two hours after administration of study medications	replacement, lumbar arthrodesis) Age - Mean (SD): Ketorolac: 41.9 (15.9); Diclofenac: 37.8 (16.8). Spain		
Christensen 2011[39]	**Ketorolac:** Ketorolac tromethamine 30 mg was administered as an intravenous (IV) bolus injection over 15 seconds into a pre-placed cannula in the arm (n=47) **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 (n=255) **Rescue analgesia:** 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	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 enrolment. Subjects 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 Age - Mean (SD): 23.7 years USA	• Pain score	

Chui 1995[40]	**Ketorolac**: Ketorolac 30mg IM 30 - 90 minutes before surgery (n=25) **Diclofenac:** Diclofenac 75mg IM 30 - 90 minutes before surgery (n=25) **Rescue analgesia:** Parenteral pethidine given if analgesia inadequate	Patients ASA I or II scheduled for elective laparoscopic sterilization Age - Mean (SD): Ketorolac: 33.5 (3.3); Diclofenac: 33.4 (4.4) Hong Kong	• Adverse events	
Forrest 2002[67]	**Ketorolac:** Ketorolac, parenteral 90 mg day for 2 days followed by oral 40 mg day for up to 7 days (n=2585) **Diclofenac:** Diclofenac, parenteral 150 mg day for 2 days followed by oral 150 mg day for up to 7 days (n=2582) **Rescue analgesia:** Opioid given (not specified)	Patients >18 years old undergoing elective major surgery Age - Mean (SD): Ketorolac: 48 ± 17; Diclofenac: 47 ± 17. 49 hospitals in eight countries across Europe	• Adverse events	
Fredman 1995[68]	**Ketorolac:** Thirty minutes prior to the end of surgery, patients received Ketorolac 60mg IM (n=19) **Diclofenac:** Thirty minutes prior to the end of surgery, patients received Diclofenac 75mg IM (n=20)	Patients ASA I or II undergoing laparoscopic cholecystectomy Age - Mean (SD): Ketorolac: 48 (16); Diclofenac: 55 (14) Israel	• Pain scores • Opioid consumption	

	Rescue analgesia: PCA device programmed to deliver 1mg bolus of morphine with a 6 minute lock out interval with no basal infusion			
Gan 2012[71]	**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 (n=82) **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 (n=173) **Rescue analgesia:** Bolus IV morphine 5 mg, titrated up to 7.5 mg after 30	Patients scheduled for abdominal or pelvic surgery Age - Mean (SD): Mean age: 43 USA	• Adverse events	

	min if analgesia was inadequate			
Jakobsson 1996[96]	**Ketorolac:** 30mg Ketorolac IM given 10 - 20 minutes before anesthesia (n=50) **Diclofenac:** 75mg Diclofenac IM given 10 - 20 minutes before anesthesia (n=50) **Rescue analgesia:** Paracetamol 1g was administered rectally as pain relief when requested. If insufficient 3 - 5 mg of IV morphine was administered	Patients ASA I scheduled for minor gynaecological surgery Age - Mean (SD): Ketorolac: 26 (7); Diclofenac: 25 (6) Sweden	• Adverse events • Length of stay	
Kostamovaara 1998[116]	**Ketorolac:** Ketorolac 30 mg as an i.v. loading dose for 30 min followed by infusion of ketorolac 90 mg over 15.5 h (n=28) **Diclofenac:** Diclofenac 75 mg i.v. loading dose for 30 min followed by infusion of diclofenac 75 mg over 15.5 h (n=28) **Rescue analgesia:** PCA fentanyl 50 µg i.v : infusion time was 5 min, lock-out time was 5 min and	Patients ASA I–III patients, aged 45–81 yr, undergoing total hip replacement Surgery Age - Median (range): Ketorolac: 65 (54-80); Diclofenac 60 (45-77). Finland	• Opioid consumption • Adverse events	

	maximum dose was 300 µg h-1			
Mony 2016[153]	**Ketorolac**: received 30mg ketorolac intramuscular injection 30 minutes preoperatively in the deltoid region (n=25) **Diclofenac**: received 75mg diclofenac sodium intramuscular injection 30 minutes preoperatively in the deltoid region (n=25) **Rescue analgesia**: Ibuprofen 400mg for rescue medication	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 Age - Other: mean age: 26.44. India	• Pain scores	
Morrow 1993[158]	**Ketorolac**: single deep intramuscular injection of ketorolac 30 mg into the upper outer quadrant of the buttock of the non-operated leg (n=36) **Diclofenac**: single deep intramuscular injection of diclofenac 75 mg into the upper outer quadrant of the buttock of the non-operated leg (n=35) **Rescue analgesia**: Intramuscular morphine (Cyclimorph '10') or oral paracetamol/codeine (Precool) at the discretion of the recovery	Patients aged 18-60 years, ASA I – II, scheduled for elective day case arthroscopy of the knee joint. Age - Mean (SD): Ketorolac: 30 (9.5); Diclofenac: 32 (10.7). Northern Ireland	• Pain scores	

	ward staff			
O'Hanlon 1996[170]	**Ketorolac**: Following induction patients were received Ketorolac 30mg IM (n=20) **Diclofenac**: Following induction patients were received Diclofenac 75mg IM (n=20) **Rescue analgesia**: Co-codamol 1g or IM Cyclimorph 0.1ml/kg	Women ASA I or II for either inpatient Diagnostic laparoscopy or laparoscopic sterilization Age - Mean (SD): Ketorolac: 30 (6.1); Diclofenac: 34 (7.7). Northern Ireland	• Pain score	
Pertunnen 1999[186]	**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 (n=10) **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 (n=10) **Rescue analgesia**: Morphine 2 mg ml–1 i.v. from a patient-controlled analgesia (PCA) device. The PCA device was programmed to provide a	Patients ASA I–III adult patients, less than 75 years of age Age - Mean (range): Ketorolac: 40.6 (18–64); Diclofenac: 50.3 (26–70). Finland	• Opioid consumption	

	bolus dose of 30g/kg–1. The lockout time was 5–10 min until the first postoperative morning and thereafter 10–12 min			
Tarkkila 1996[228]	**Ketorolac**: After induction of anesthesia, before surgical incision, the patients received IV Ketorolac Tromethamine o.4mg/kg in 100ml 0.9% sodium chloride. The same IV dose was given three times at six hour intervals (n=30) **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 (n=30) **Rescue analgesia**: Oxycodone 0.03mg/kg (four hour maximum dose 0.4mg/kg and lock out period of 5 minutes was administered via PCA	Patients ASA I-II patients scheduled for maxillofacial surgery Mean age (SD): ketorolac: 30 ± 9; Diclofenac: 33 ± 11 Finland	• Opioid consumption • Adverse events	
Tarkkila 1999[227]	**Ketorolac**: After induction of anesthesia before surgical incision patients received Ketorolac 30mg as an	Patients ASA I–II patients, aged 16–50 yr, undergoing elective tonsillectomy	• Adverse events	

	IV infusion. In the ketorolac group, the same i.v. dose was repeated twice at 6-h intervals. Duration intraoperatively to POD1 (n=20) **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 (n=20) **Rescue analgesia**: 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)	Age - Mean (SD): Ketorolac: 31 (8); Diclofenac: 30 (10) Finland		
Walton 1993[242]	**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 (n=101) **Diclofenac**: Single intramuscular 3 ml injection of 75 mg in the lateral	Adults aged 16-65 years having surgery for the extraction of impacted lower third molars, possibly involving bone removal under general anaesthetic. Age - Mean (range): Adults aged 16-65 years. United Kingdom	• Pain scores • Opioid consumption • Adverse events	

	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 (n=50) **Rescue analgesia**: Paracetamol was used as rescue medication throughout trial			
Cox-2 inhibitors compared to NSAIDs				
Parecoxib compared to ketorolac				
Barton 2002[22]	**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 (n=41) **Parecoxib:** 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	Women aged 18–64 year requiring parenteral analgesia for moderate or severe pain after elective total abdominal hysterectomy or myomectomy, but who were otherwise generally healthy Age - Mean (range): Ketorolac: 40.8 (27-52); Parecoxib: 42.8 (21-65). USA	• Adverse events	

	after discontinuation of patient-controlled analgesia were then randomized to receive one intravenous dose of Parecoxib (20 or 40mg) (n=77) **Rescue analgesia:** 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			
Bikhazi 2004[28]	**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 (n=42) **Parecoxib:** Within 6 hours of discontinuing PCA, patients were given 20 OR 40mg Parecoxib IV. Study medication was readministered as required at 6 hour intervals	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 anaesthesia. Age - Mean (SD): Ketorolac: 44.7 (8.2); Parecoxib: 41.56 (7.58). USA	• Adverse events	

	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 (n=81) **Rescue analgesia:** Unclear, only non-study medications were given (as rescue medications) before the second administration of study medications			
Daniels 2001[47]	**Ketorolac:** Ketorolac 60mg IM, after developing moderate to severe postoperative pain after oral surgery (n=51) **Parecoxib:** Parecoxib 20mg or 40mg IM, after developing moderate to severe postoperative pain after oral surgery (n=101) **Rescue analgesia:** Not specified	Patients aged 18-64; undergoing extraction of ≥ 2 impacted third molars (≥1 of which was mandibular) requiring bone removal. Before enrolment patients had to be experiencing moderate to severe pain on visual analogue scale within 6 hours of surgery. Age - Other: (Mean age) Ketorolac: 22.5; Parecoxib: 21.4 USA	• Adverse events	
Leykin 2008[128]	**Ketorolac**: 30mg of Ketorolac 15 minutes prior to the end of intraoperative remifentanil infusion (n=25) **Parecoxib**:	Patients ASA I - II, aged 18 - 65, undergoing functional endoscopic sinus surgery / Turbinate surgery Age - Mean (SD): Ketorolac: 35 (11); Parecoxib: 32 (10).	• Pain score • Opioid consumption • Adverse events	

	40mg of Parecoxib 15 minutes prior to the end of intraoperative remifentanil infusion (n=25) **Rescue analgesia**: IV morphine 2mg at 10 minute intervals until pain was resolved and 2g IV proparacetamol once left from PACU	Italy		
Mehlisch 2003[139]	**Ketorolac**: 30mg of Ketorolac, within 6 hours of surgery completion and having moderate or severe postoperative pain (n=50) **Parecoxib**: 20mg, 50mg, or 100mg or Parecoxib, within 6 hours of surgery completion and having moderate or severe postoperative pain (n=153) **Rescue analgesia**: Acetaminophen PO 1000mg; Lortab PO (Hydrocodone 5mg + acetaminophen 500mg) Lortab PO (Hydrocodone 7.5mg + acetaminophen 500mg) Demerol (IM - Meperidine 50mg) Phenergan (25mg Promethazine)	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. Age - Other: Mean age: Ketorolac: 22.5; Parecoxib: 23.6. USA	• Adverse events	
Mehlisch 2004[140]	**Ketorolac**:	Patients aged 18 - 45 years,	• Pain scores	

	Ketorolac 30mg IM if pain was ≥50mm on VAS within 6 hours after surgery (n=51) **Parecoxib**: Parecoxib 20mg IM if pain was ≥50mm on VAS within 6 hours after surgery (n=50) **Rescue analgesia**: Oral acetaminophen 1,000 mg, oral hydrocodone 5 mg, plus acetaminophen 500 mg, oral hydrocodone 7.5 plus acetaminophen 500mg or IM meperidine 50 mg plus promethazine 25mg	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. Age - Other: mean age: Ketorolac: 24; Parecoxib: 23.8 USA		
Ng 2004[165]	**Ketorolac**: Ketorolac 30 mg i.v., at induction of anaesthesia (n=18) **Parecoxib**: Parecoxib 40 mg i.v. at induction of anaesthesia (n=18) **Rescue analgesia**: Co-codamol 30/500 (codeine phosphate 30 mg, acetaminophen 500 mg) for mild to moderate pain, and morphine 10 mg i.m. for severe pain	Patients aged 20-50 yr and undergoing laparoscopic sterilization Age - Mean (range): Ketorolac: 35 (32-38); Parecoxib: 34 (29-38). United Kingdom	• Pain scores • Adverse events	
Siribumrungwong 2015[208]	**Ketorolac**: The ketorolac group received 30 mg of ketorolac	patients who were diagnosed as lumbar disc herniation, spondylolisthesis, spinal	• Pain scores • Opioid consumption • Adverse events	

	intravenously. All patients received their medication 30 minutes before surgery from the anaesthesiologist (n=32) **Parecoxib**: The praecox group received 40 mg of parecoxib intravenously. All patients received their medication 30 minutes before surgery from the anaesthesiologist (n=32) **Rescue analgesia**: paracetamol (500 mg) and intravenous morphine for rescue postoperative pain control	stenosis, and had indications for decompressive laminectomy and fusion for one to three levels; 18–80 years; ASA of I-II Age - Mean (SD): Ketorolac: 58.2 ± 9.5; Parecoxib: 58 ± 8.6 Thailand		
Wong 2010[251]	**Ketorolac**: received a loading intravenous bolus of 30 mg ketorolac, then 90 mg ketorolac combined with morphine in a PCA fashion throughout the study course (n=33) **Parecoxib**: When the parturient were transferred to Post-Anesthesia Recovery Room, 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	Patients aged 20 and 40 years of age, of ASA physical status I or II, weighing 60e90 kg, and standing 155-170 cm. Age - Mean (SD): Ketorolac: 30.7 ± 4.4; Parecoxib: 30.8 ± 5.6 Taiwan	• Pain scores • Adverse events • Length of stay	

	48-h intervals, after the initial dose. (n=33) **Rescue analgesia**: 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)			
Celecoxib compared to diclofenac				
Argoff 2016[12]	**Diclofenac:** Patients who reported pain intensities ≥40mm were randomized to receive either low-dose SoluMatrix diclofenac 18mg or 35mg capsules three times daily (n=216) **Celecoxib:** Patients who reported pain intensities ≥40mm were randomized to receive celecoxib 400mg loading dose followed by 200-mg capsules twice daily (n=106) **Rescue analgesia:** 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	Patients 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 Age - Mean (SD): 39.7 ± 12.0 years USA	• Adverse events	

Manvelian 2012[133]	**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 (n=100) **Celecoxib**: Celecoxib 400mg in subjects who experienced moderate to severe pain intensity (a score of ≥ 50 mmon a 100 mmVAS) within 6 hours after surgery (n=51) **Rescue analgesia**: acetaminophen 1,000 mg	Patients ≥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 Age - Mean (SD): Diclofenac: 22.2 ± 4.9; Celecoxib: 22.7 ± 3.3 USA	• Pain scores	
Wattchow 2009[244]	**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. (n=69) **Celecoxib**: 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	Patients who will 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 - Mean (SD): Diclofenac: 59 ± 14; Celecoxib: 65 ± 14	• Pain scores • Adverse events • Length of stay	

	day. (n=74) **Rescue analgesia**: 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	Australia		
Celecoxib compared to ibuprofen				
Al-Sukhan 2012[9]	**Ibuprofen:** 200mg Ibuprofen 1 hour before surgery (n=45) **Celecoxib:** 200mg Celecoxib 1 hour before surgery (n=48) **Rescue analgesia:** 1g paracetamol as rescue medication if needed	Patients ASA I, aged 18 - 72, scheduled to undergo surgical removal of an impacted mandibular third molar Age - Mean (SD): Ibuprofen: 29.1 (7.9); Celecoxib: 30.3 (5.5) Finland	• Pain scores	
Akinbade 2018[7]	**Ibuprofen:** Ibuprofen 400mg every 8 hours as needed for 48 hours as needed. Amoxicillin 500mg 8 hourly and metronidazole 400mg 8 hourly for 5 days (n=45) **Celecoxib:** Celecoxib 400mg to start and then 200mg every 12 hours for	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. Mean age (SD): Ibuprofen: 27.22 (7.13);	• Pain scores	

	48 hours as needed. Amoxicillin 500mg 8 hourly and metronidazole 400mg 8 hourly for 5 days (n=45)	Celecoxib: 26.56 (6.29) Nigeria		
Al-Sukhan 2011[10]	**Ibuprofen:** 400mg Ibuprofen 1 hour before surgery (n=162) **Celecoxib:** 200mg Celecoxib 1 hour before surgery (n=147) **Rescue analgesia:** 1g of paracetamol as rescue medication if needed	Patients ASA I scheduled to undergo surgical removal of a mandibular molar ASA I scheduled to undergo surgical removal of a mandibular molar Finland	• Adverse events	
Cheung 2007[37]	**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 (n=57) **Celecoxib:** 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 (n=57)	Patients above 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. Age - Mean (SD): Ibuprofen: 22.0 (4.7); Celecoxib: 21.4 (4.2). USA	• Pain scores • Adverse events	

	Rescue analgesia: Rescue analgesia given but not stated			
Doyle 2002[58]	**Ibuprofen:** Ibuprofen liquate capsules 400mg (n=74) **Celecoxib:** Celecoxib 200mg (n=74) **Rescue analgesia:** Given but not specified	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 - Mean (SD): Ibuprofen: 21.8 (6.0); Celecoxib: 21.1 (4.8). USA	• Adverse events	
White 2011[248]	**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 (n=60) **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. (n=60)	patients scheduled for superficial (noncavitary) surgical procedures (e.g., hernia repair, partial mastectomy, or joint arthroscopy) Age - Mean (SD): Ibuprofen: 50 ± 13; Celecoxib: 48 ± 13 USA	• Pain scores • Adverse events • Functional measure	

	Rescue analgesia: Patients complaining of moderate-to-severe pain (VRS score≥4) were treated with hydromorphone, 0.1 to 0.2 mg IV.			
Celecoxib and ketorolac				
Ulm 2017[235] merged with Ulm 2018[236]	**Ketorolac**: Ketorolac during surgery 30 mg intravenous and then 6 hourly for 48 hours or until discharge (n=70) **Celecoxib**: Celecoxib 1 hour before surgery at 400 mg and followed by postoperative oral celecoxib 200 mg twice daily for 7 days following discharge (n=68) **Rescue analgesia**: 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.	Patients undergoing robotic hysterectomy Age - Mean (SD): Ketorolac group: 56.3 (11.3), Celecoxib group: 55.1 (14.4). USA	• Pain scores • Opioid consumption	

See appendices for full evidence tables

2.9.4 Quality assessment of clinical studies included in the evidence review

Table 25: Clinical evidence summary: Naproxen versus Ibuprofen

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Ibuprofen	Risk difference with Naproxen (95% CI)
TOTPAR 6 hours	323 (2 studies) 6 hours	⊕⊕⊕⊖ MODERATE1,2 due to risk of bias		The mean totpar 6 hours in the control groups was 10.6	The mean totpar 6 hours in the intervention groups was 1.07 higher (0.72 lower to 2.86 higher)
TOTPAR >6-24h hours	323 (2 studies)	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean totpar >6-24h hours in the control groups was 16.8	The mean totpar >6-24h hours in the intervention groups was 3.65 higher (0.13 to 7.17 higher)
Pain relief (50% resolved)	162 (1 study) 24 hours	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean pain relief (50% resolved) in the control groups was 0.4	The mean pain relief (50% resolved) in the intervention groups was 0 higher (0.11 lower to 0.11 higher)

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 26: Clinical evidence summary: Ketorolac versus Diclofenac

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diclofenac	Risk difference with Ketorolac (95% CI)
Pain score ≤6 hours	160 (3 studies)	⊕⊕⊕⊖ MODERATE1 due to inconsistency		The mean pain score ≤6 hours in the control groups was 1.74	The mean pain score ≤6 hours in the intervention groups was 0.09 lower (0.5 lower to 0.33 higher)
Pain score >6-24 hours	50 (1 study) 24 hours hours	⊕⊕⊖⊖ LOW2,3 due to risk of bias, imprecision		The mean pain score >6-24 hours in the control groups was 0.25	The mean pain score >6-24 hours in the intervention groups was 0.11 lower (0.39 lower to 0.17 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diclofenac	Risk difference with Ketorolac (95% CI)
Dose of Opioid ≤6 hours	155 (3 studies) 6 hours	⨁⨁⨁⨀ MODERATE2 due to risk of bias			The mean dose of opioid ≤6 hours in the intervention groups was 0.17 standard deviations lower (0.49 lower to 0.14 higher)
Dose of Opioid 6-24 hours	136 (3 studies)	⨁⨁⨀⨀ LOW2,3 due to risk of bias, imprecision			The mean dose of opioid 6-24 hours in the intervention groups was 0.36 standard deviations higher (0.1 lower to 0.81 higher)
Total Pain Relief (TOTPAR6)	378 (2 studies) 6 hours	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean total pain relief (totpar6) in the control groups was 288.9	The mean total pain relief (totpar6) in the intervention groups was 74.95 higher (35.24 to 114.66 higher)
Mortality	5144 (1 study) Postoperative	⨁⨁⨀⨀ LOW3 due to imprecision	RR 1.79 (0.6 to 5.35)	Moderate	
				2 per 1000	2 more per 1000 (from 1 fewer to 9 more)
Acute Kidney Injury	5144 (1 study) Postoperative	⨁⨁⨀⨀ LOW3 due to imprecision	RR 0.5 (0.09 to 2.72)	Moderate	
				2 per 1000	1 fewer per 1000 (from 2 fewer to 3 more)
Surgical site bleed	5144 (1 study) Postoepratively	⨁⨁⨀⨀ LOW3 due to imprecision	RR 1.05 (0.67 to 1.64)	Moderate	
				14 per 1000	1 more per 1000 (from 5 fewer to 9 more)
Gastrointestinal bleed	5144 (1 study) Postoperative	⨁⨁⨀⨀ LOW3 due to imprecision	RR 0.33 (0.01 to 8.15)	Moderate	
				0 per 1000	-
Allergic reaction	5144 (1 study) Postoperative	⨁⨁⨀⨀ LOW3 due to imprecision	RR 1 (0.2 to 4.93)	Moderate	
				1 per 1000	0 fewer per 1000 (from 1 fewer to 4 more)
Nausea	463	⨁⨁⨀⨀	RR 1.04	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diclofenac	Risk difference with Ketorolac (95% CI)
	(5 studies) Postoperative	LOW3 due to imprecision	(0.78 to 1.39)	321 per 1000	13 more per 1000 (from 71 fewer to 125 more)
Vomiting	463 (5 studies) Postoperative	⨁⨁⨁⨀ MODERATE3 due to imprecision	RR 1.34 (0.82 to 2.18)	Moderate	
				100 per 1000	34 more per 1000 (from 18 fewer to 118 more)
Nausea & Vomiting	110 (2 studies) Postoperative	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	RR 1.23 (0.68 to 2.21)	Moderate	
				253 per 1000	58 more per 1000 (from 81 fewer to 306 more)
Itching	363 (4 studies) stoperative	⨁⨁⨀⨀ LOW3 due to imprecision	RR 0.77 (0.39 to 1.5)	Moderate	
				137 per 1000	32 fewer per 1000 (from 84 fewer to 68 more)
Headache	208 (1 study) Postoeprative	⨁⨁⨀⨀ LOW2,3 due to risk of bias, imprecision	RR 1.84 (0.96 to 3.55)	Moderate	
				114 per 1000	96 more per 1000 (from 5 fewer to 291 more)
Other adverse events	5345 (3 studies) Postoperative	⨁⨀⨀⨀ VERY LOW1,3 due to inconsistency, imprecision	RR 0.83 (0.24 to 2.82)	Moderate	
				32 per 1000	5 fewer per 1000 (from 24 fewer to 58 more)
Length of stay (hours)	100 (1 study) Postoperative	⨁⨁⨁⨀ MODERATE3 due to imprecision		The mean length of stay (hours) in the control groups was 109 hours	The mean length of stay (hours) in the intervention groups was 2 lower (12.58 lower to 8.58 higher)

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 27: Clinical evidence summary: Diclofenac versus Ibuprofen

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Ibuprofen	Risk difference with Diclofenac (95% CI)
Pain score ≤ 6 hours	163 (1 study)	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean pain score 6 hours in the control groups was 2.98	The mean pain score 6 hours in the intervention groups was 0.06 higher (0.72 lower to 0.84 higher)

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 28: Clinical evidence summary: Ibuprofen versus Ketorolac

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Ketorolac	Risk difference with Ibuprofen (95% CI)
Dose of Opioid <6 hours	51 (1 study)	⊕⊕⊕⊕ HIGH		The mean dose of opioid <6 hours in the control groups was 19.92 Milligrams	The mean dose of opioid <6 hours in the intervention groups was 14.39 lower (20.47 to 8.31 lower)

Table 29: Clinical evidence summary: Ketorolac versus Parecoxib

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parecoxib	Risk difference with Ketorolac (95% CI)
Pain score <6 hours	64 (1 study)	⊕⊕⊕⊖ MODERATE1 due to imprecision		The mean pain score <6 hours in the control groups was 6	The mean pain score <6 hours in the intervention groups was 0.3 lower (1.27 lower to 0.67 higher)
Pain score 6-24 hours	64	⊕⊕⊕⊖		The mean pain score 6-24 hours	The mean pain score 6-24 hours in

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parecoxib	Risk difference with Ketorolac (95% CI)
	(1 study)	MODERATE1 due to imprecision		in the control groups was 5	the intervention groups was 0.3 lower (1.29 lower to 0.69 higher)
TOTPAR 6 hours	101 (1 study)	⨁⨁⨁⊖ MODERATE1 due to imprecision		The mean totpar 6 hours in the control groups was 12.6	The mean totpar 6 hours in the intervention groups was 2 higher (1.06 lower to 5.06 higher)
TOTPAR 24hours	101 (1 study)	⨁⨁⨁⊖ MODERATE1 due to imprecision		The mean totpar 24hours in the control groups was 47	The mean totpar 24hours in the intervention groups was 7.6 lower (19.43 lower to 4.23 higher)
Dose of Opioid ≤6 hours	50 (1 study)	⨁⨁⊖⊖ LOW1 due to imprecision		The mean dose of opioid 6 hours in the control groups was 5	The mean dose of opioid 6 hours in the intervention groups was 0 higher (1.25 lower to 1.25 higher)
Dose of Opioid 6 - 24 hours	64 (1 study)	⨁⨁⨁⊖ MODERATE1 due to imprecision		The mean dose of opioid 6 - 24 hours in the control groups was 4.9	The mean dose of opioid 6 - 24 hours in the intervention groups was 1.5 higher (1.4 lower to 4.4 higher)
Nausea	473 (3 studies) Postoperative	⨁⨁⨁⊖ MODERATE1 due to imprecision	RR 1.37 (0.96 to 1.95)	Moderate	
				150 per 1000	56 more per 1000 (from 6 fewer to 143 more)
Vomiting	539 (4 studies) Postoperative	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.38 (0.81 to 2.35)	Moderate	
				55 per 1000	21 more per 1000 (from 10 fewer to 74 more)
Nausea & Vomiting	180 (3 studies) Postoperative	⨁⨁⊖⊖ LOW1 due to imprecision	RR 0.88 (0.49 to 1.59)	Moderate	
				121 per 1000	15 fewer per 1000 (from 62 fewer to 71 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parecoxib	Risk difference with Ketorolac (95% CI)
Abdominal Pain	437 (4 studies) Postoperative	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	Peto odds 0.89 (0.43 to 1.87)	Moderate 93 per 1000	10 fewer per 1000 (from 53 fewer to 81 more)
Headache	421 (3 studies) Postoperative	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.49 (0.82 to 2.71)	Moderate 78 per 1000	38 more per 1000 (from 14 fewer to 133 more)
Pruritis	152 (1 study) Postoperative	⊕⊕⊕⊖ MODERATE1 due to imprecision	Peto odds 19.7 (0.31 to 1250.54)	Moderate 0 per 1000	Not estimable
Length of stay	66 (1 study) Postoperative	⊕⊕⊕⊖ MODERATE2 due to risk of bias		The mean length of stay in the control groups was 6 days	The mean length of stay in the intervention groups was 0 higher (0.31 lower to 0.31 higher)

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 30: Clinical evidence summary: Diclofenac versus Celecoxib

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Celecoxib	Risk difference with Diclofenac (95% CI)
TOTPAR 6 hours	151 (1 study)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean totpar 6 hours in the control groups was 5.71	The mean totpar 6 hours in the intervention groups was 2.41 higher (0.8 to 4.02 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Celecoxib	Risk difference with Diclofenac (95% CI)
TOTPAR 6-24 hours	151 (1 study)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean totpar 6-24 hours in the control groups was 14.61	The mean totpar 6-24 hours in the intervention groups was 2.69 higher (2.19 lower to 7.57 higher)
Nausea	322 (1 study) Postoperative	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1 (0.68 to 1.46)	Moderate	
				274 per 1000	0 fewer per 1000 (from 88 fewer to 126 more)
Vomiting	465 (2 studies) Postoperative	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.95 (0.63 to 1.44)	Moderate	
				179 per 1000	9 fewer per 1000 (from 66 fewer to 79 more)
Dizziness	322 (1 study) postoperative	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.98 (0.49 to 1.95)	Moderate	
				104 per 1000	2 fewer per 1000 (from 53 fewer to 99 more)
Headache	322 (1 study) postoperative	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.25 (0.65 to 2.41)	Moderate	
				104 per 1000	26 more per 1000 (from 36 fewer to 147 more)
Pruritis	322 (1 study) postoperative	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.23 (0.39 to 3.82)	Moderate	
				38 per 1000	9 more per 1000 (from 23 fewer to 107 more)

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.

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Table 31: Clinical evidence summary: Ibuprofen versus Celecoxib

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Celecoxib	Risk difference with Ibuprofen (95% CI)
Pain score ≤6 hours	205 (2 studies)	⨁⨁⨁⨁ HIGH1		The mean pain score ≤6 hours in the control groups was 2.5	The mean pain score ≤6 hours in the intervention groups was 0.23 higher (0.35 lower to 0.81 higher)
Pain score 6-24 hours	205 (2 studies)	⨁⨁⨁⨁ HIGH1		The mean pain score 6-24 hours in the control groups was 3.7	The mean pain score 6-24 hours in the intervention groups was 0.24 higher (0.52 lower to 1 higher)
TOTPAR (6 hours)	46 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean totpar (6 hours) in the control groups was 13.4	The mean totpar (6 hours) in the intervention groups was 1.5 higher (2.14 lower to 5.14 higher)
TOTPAR (24 hours)	46 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean totpar (24 hours) in the control groups was 48.8	The mean totpar (24 hours) in the intervention groups was 10.5 lower (28.09 lower to 7.09 higher)
Nausea	623 (4 studies) postoeprative	⨁⨁⨀⨀ LOW1 due to imprecision	RR 1.05 (0.72 to 1.53)	Moderate	
				95 per 1000	5 more per 1000 (from 27 fewer to 50 more)
Vomiting	314 (3 studies) postoperative	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.99 (0.36 to 2.77)	Moderate	
				17 per 1000	0 fewer per 1000 (from 11 fewer to 30 more)
Headache	566 (4 studies) postoperativ	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias,	Peto OR 0.48 (0.26 to	Moderate	
				339 per 1000	176 fewer per 1000 (from 41 fewer to 251 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Celecoxib	Risk difference with Ibuprofen (95% CI)
	e	inconsistency, imprecision	0.88)		
Time to ambulation (minutes)	120 (1 study) postoperative	⨁⨁⨁⊖ MODERATE1 due to imprecision		The mean time to ambulation (minutes) in the control groups was 92 minutes	The mean time to ambulation (minutes) in the intervention groups was 4 lower (14.02 lower to 6.02 higher)

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 32: Clinical evidence summary: Ketorolac versus Celecoxib

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Celecoxib	Risk difference with Ketorolac (95% CI)
Pain score 6 - 24 hours	138 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain score 6 - 24 hours in the control groups was 2.4	The mean pain score 6 - 24 hours in the intervention groups was 0.3 higher (0.29 lower to 0.89 higher)
Dose of Opioid 6 - 24h	414 (1 study)	⨁⨁⨁⊖ MODERATE1 due to risk of bias		The mean dose of opioid 6 - 24h in the control groups was 2.2	The mean dose of opioid 6 - 24h in the intervention groups was 0.07 lower (0.36 lower to 0.22 higher)

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

See appendices for full GRADE tables

Table 33: Evidence not suitable for GRADE

Outcome	Study (no. of participants)	Risk of bias	Comparison results	Intervention results	*P* value
Pain score ≤6 hours VAS (0-100)	36 participants Ng 2004 [165]	High	Median (IQR) Parecoxib: 5 (0-28)	Median (IQR) Ketorolac:11 (1-28)	0.01
	60 participants Joshi 2004 [103]	Very high	Median (range) Ibuprofen: 31 (0-100)	Median (range) Diclofenac: 33 (0-100)	
Pain score ≤6 hours Area under Curve	50 participants Leykin 2008 [128]	Low	Median (range) Ketorolac: 1.858 (0.078 - 5.281)	Median (range) Parecoxib: 1.764 (0.072-3.925)	
	147 participants Walton 1993 [242]	High	Mean Ketorolac: 60.0	Mean Diclofenac: 61.9	0.0029
Pain score ≥6 – 24 hours (VAS 0-10)	66 participants Wong 2010 [251]	High	Median (range) Parecoxib: 3.1 (0-5)	Median (range) Ketorolac: 4.3 (0-8)	0.005
	40 participants O'Hanlon 1996 [170]	High	Median (IQR) Diclofenac: 2.1 (2.6)	Median (IQR) Ketorolac: 2.1 (2.7)	
Total Pain relief ≥6 – 24 Scale 0-48	93 participants Al-Sukhan 2012 [9]	Very High	Median (range) Ibuprofen: 16.9 (14.0-19.3)	Median (range) Celecoxib: 27.1 (24.0-29.7)	
Pain score ≥6 – 24 hours Area under Curve	50 participants Leykin 2008 [128]	Low	Median (range) Ketorolac: 2.306 (1.285-4.434)	Median (range) Parecoxib: 1.986 (0.875-3.889)	

Outcome	Study (no. of participants)	Risk of bias	Comparison results	Intervention results	*P* value
Nausea	36 participants Ng 2004[165]	High	Median (IQR) Parecoxib: 0 (0-0)	Median (IQR) Ketorolac: 2 (0-5)	0.121

2.10 Economic evidence.

Please see section 2.5.

2.11 Evidence statements

2.11.1 Clinical evidence statements

No outcomes were reported for health related quality of life or the following important outcomes; psychological distress and mental well-being, symptom scores,length of stay in intensive care and hospital readmission.

Naproxen versus Ibuprofen

Pain relief

Two studies showed no clinically important difference with the total pain relief up to six hours between Naproxen versus Ibuprofen postoperatively (2 studies, n=323, moderate quality evidence)

Two studies showed a clinically important benefit with Naproxen for total pain relief from six to twenty four hours postoperatively compared to ibuprofen (2 studies, n=323, moderate quality of evidence)

One study showed no clinically important difference for Naproxen versus Ibuprofen when assessing fifty percent of pain resolved pain relief (1 study, n=162, moderate quality evidence)

Ketorolac versus Diclofenac

Pain relief

Three studies showed no clinically important difference for pain scores under six hours between ketorolac and diclofenac (3 studies, n=160, moderate quality evidence)

One study showed no clinically important difference for pain scores from six to twenty four hours between ketorolac and diclofenac (1 study, n=50, low quality evidence)

Two studies showed a clinically important benefit with ketorolac for total pain relief at six hours postoperatively compared to diclofenac (2 studies, n=378, very low quality evidence)

Rescue medication

Three studies showed no clinically important difference between ketorolac and diclofenac in the dose of opioid used up to 6 hours postoperatively (3 studies, n=155, moderate quality of evidence)

Three studies showed no clinically important difference between ketorolac and diclofenac in the dose of opioid used from six to twenty four hours postoperatively (3 studies, n=136, moderate low quality of evidence)

Adverse events

One study showed no clinically important difference between ketorolac and Diclofenac (1 study, n=5144, low quality evidence)

One study showed no clinically important difference between ketorolac and diclofenac for acute kidney injury (1 study, n=5144, low quality of evidence)

One study which showed no clinically important difference between ketorolac and diclofenac for surgical site bleed (1 study, n=5144, low quality of evidence)

One study was not estimable for gastrointestinal bleed between ketorolac and diclofenac (1 study, n=5144, low quality of evidence)

One study showed no clinically important difference between ketorolac and diclofenac for rates of allergic reaction (1 study, n=5144, low quality of evidence)

Five studies which assessed nausea found no clinically important difference between Ketorolac and Diclofenac (5 studies, n=463, low quality evidence)

Five studies found no clinically important difference between Ketorolac and Diclofenac for rates of vomiting (5 studies, n=463, low quality evidence)

Two studies found no clinically important difference in nausea and vomiting together between ketorolac and diclofenac (2 studies, n=110, very low quality evidence)

Four studies found no clinically important difference in rates of itching between Ketorolac and Diclofenac (4 studies, n=363, low quality evidence)

One study showed no clinically important difference in rates of headache between ketorolac and diclofenac (1 study, n=208, low quality evidence)

Three studies showed no clinically important difference between ketorolac and diclofenac in rates of other adverse events (3 studies, n=5345, very low quality evidence)

Length of stay

One study found no clinically important difference in length of stay between Ketorolac and Diclofenac (1 study, n=100, moderate quality of evidence)

Diclofenac vs Ibuprofen

Pain relief

One study found no clinically important difference between Diclofenac and Ibuprofen when assessing postoperative pain scores at six hours (1 study, n=163, moderate quality evidence)

Ibuprofen vs Ketorolac

Rescue medication

One study found a clinically important benefit with Ibuprofen in the dose of opioid used under six hours postoperatively compared to Ketorolac (1 study, n=51, high quality evidence)

Ketorolac vs Parecoxib

Pain relief

One study found no clinically important difference in postoperative pain scores at under six hours between Ketorolac and Parecoxib (1 study, n=64, moderate quality evidence)

One study found no clinically important difference in postoperative pain scores at under six hours between Ketorolac and Parecoxib (1 study, n=64, moderate quality evidence)

One study found no clinically important difference in total pain relief at under six hours between ketorolac and parecoxib (1 study, n=101, moderate quality evidence)

One study found clinically important harm with Ketorolac in total pain relief from six to twenty four hours compared to Parecoxib (1 study, n=101, moderate quality evidence)

Rescue medication

One study found no clinically important difference assessing the dose of opioid used at 6 hours postoperatively between ketorolac and diclofenac (1 study, n=50, low quality evidence)

One study found no clinically important difference in the dose of opioids used from six to twenty four hours postoperatively between ketorolac and diclofenac (1 study, n=64, moderate quality evidence)

Adverse events

Three studies assessing nausea found no clinically important difference between ketorolac and parecoxib (3 studies, n=473, moderate quality evidence)

Four studies found no clinically important difference in vomiting rates between ketorolac and parecoxib (4 studies, n=539, very low quality evidence)

Three studies showed no clinically important difference in nausea and vomiting between ketorolac and parecoxib (3 studies, n=180, low quality of evidence)

Four studies found no clinically important difference in rates of abdominal pain between ketorolac and parecoxib (4 studies, n=437, very low quality)

Three studies assesses rated of headache and found no clinically important difference between ketorolac and parecoxib (3 studies, n=421, very low quality of evidence)

One study which assessed pruritus could not estimate an absolute effect (1 study, n=152, moderate quality evidence)

Length of stay

One study found no clinically important difference in length of stay between ketorolac and parecoxib (1 study, n=66, moderate quality evidence)

Diclofenac vs Celecoxib

Pain relief

One study found no clinically important difference in total pain relief at six hours postoperatively between diclofenac and celecoxib (1 study, n=151, low quality evidence)

One study found no clinically important difference in total pain relief from six to twenty four hours postoperatively between diclofenac and celecoxib (1 study, n=151, low quality evidence)

One study showed no clinically important difference in rates of nausea between diclofenac and celecoxib (1 study, n=322, low quality evidence)

Two studies showed no clinically important difference in vomiting between diclofenac and celecoxib (2 studies, n=465, very low quality evidence)

One study showed no clinically important difference in rates of dizziness between diclofenac and celecoxib (1 study, n=322, low quality evidence)

One study showed no clinically important difference in rates of headache between diclofenac and celecoxib (1 study, n=322, low quality evidence)

One study showed no clinically important difference in rates of pruritus between diclofenac and celecoxib (1 study, n=322, low quality evidence)

Ibuprofen vs Celecoxib

Pain relief

Two studies found no clinically important difference in pain score under six hours between Ibuprofen and Celecoxib (2 studies, n=205, high quality evidence)

Two studies found no clinically important difference in pain scores from six to twenty four hours between Ibuprofen and Celecoxib (2 studies, n=205, high quality evidence)

One study assessing total pain relief at six hours found no clinically important difference between ibuprofen and Celecoxib (1 study, n=46, very low quality evidence)

One study assessing total pain relief from six to twenty four hours found no clinically important difference between ibuprofen and Celecoxib (1 study, n=46, very low quality evidence)

Adverse events

Four studies found no clinically important difference in rates of nausea between ibuprofen and Celecoxib (4 studies, n=623, low quality evidence)

Three studies assessing rates of vomiting found no clinically important difference between ibuprofen and Celecoxib (3 studies, n=314, very low quality)

Four studies found a clinically important with ibuprofen benefit in rates of headache compared to Celecoxib (4 studies, n=566, very low quality)

Functional measures

One study assessing the postoperative time to ambulation (minutes) found no clinically important difference between ibuprofen and celecoxib (1 study, n=120, moderate quality of evidence)

Ketorolac vs Celecoxib

Pain relief

One study found no clinically important difference in pain scores between six and twenty four hours postoperatively between ketorolac and celecoxib (1 study, n=138, low quality evidence)

Rescue medication

One study assessing the dose of opioid used between six and twenty four hours postoperatively found no clinically important difference between ketorolac and celecoxib (1 study, n=414, moderate quality evidence)

Evidence not suitable for GRADE

Parecoxib vs Ketorolac

Pain relief

One study showed a statistically significant benefit with parecoxib for pain score under six hours compared to ketorolac (1 study) n=36, high risk of bias)

One study assessing pain score with area under the curve under six hours showed a trend to benefit with ketorolac compared to parecoxib (1 study, n=50, low risk of bias)

One study showed a trend to benefit with ketorolac assessing pain score with area under the curve from six to twenty four hours compared to parecoxib (1 study, n=50, low risk of bias)

One study showed a statistically significant benefit with ketorolac for pain score from six to twenty four hours compared to parecoxib (1 study, n=66, high risk of bias)

Adverse events

One study found no clinically important difference in rates of nausea between parecoxib and ketorolac (1 study, n=36, high risk of bias)

Ibuprofen vs Diclofenac

One study assessing pain score under six hours found no notable difference in pain scores between Ibuprofen and Diclofenac (1 study, n=60, very high risk of bias)

Diclofenac vs Ketorolac

One study showed a statistically significant difference between diclofenac for pain scores less than six hours postoperatively compared to ketorolac (1 study, n=66, high risk of bias)One study found no notable difference between diclofenac and ketorolac in pain scores from six to twenty four hours (1 study, n=40, high risk of bias)

Ibuprofen vs Celecoxib

One study showed a trend to benefit with ibuprofen for total pain relief from six to twenty four hours compared to Celecoxib (1 study, n=93, very high risk of bias)

3 Opioid

3.1 Review question 1: What is the clinical and cost effectiveness of IV opioid compared to oral opioid given post operatively in managing acute post-operative pain?

3.2 PICO table

For full details see the review protocol in appendices.

Table 34: PICO characteristics of review question

Population	Adults (18 years and older) who have undergone surgery.
Interventions	• IV (PCA) opioid

Comparisons	• Oral opioid
	  ○ Immediate release
	  ○ Modified release

Outcomes	CRITICAL:
	• health-related quality of life
	• pain reduction
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• amount of additional medication use
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• adverse events (including respiratory depression, nausea, vomiting)
	IMPORTANT:
	• psychological distress and mental well-being
	• symptom scores
	• functional measures
	• length of stay in intensive care
	• length of stay in hospital
	• hospital readmission

Study design	Randomised controlled trials and systematic reviews of randomised controlled trials.

3.3 Clinical evidence

3.3.1 Included studies

Six randomised controlled trials were included in the review;[49 56 172 195 200 216] these are summarised in table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See appendices for the study selection flow chart, study evidence tables, forest plots and GRADE tables.

3.3.2 Excluded studies

See the excluded studies list in appendices.

3.3.3 Summary of clinical studies included in the evidence review

Table 35: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Davis 2006[49]	**IV PCA:** 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. N=47 **Oral opioid (immediate release):** 2 tablets of oxycodone-acetaminophen immediately after completion of caesarean 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	All patients aged ≥18 years in Labour and Delivery for planned caesarean delivery. Mean age (SD): PCA – 31.5 (4.7) Oral – 31.9 (4.5) USA	• Pain score (VAS) 6 h • Pain score (VAS) 24 h • Adverse events (nausea) 6h • Adverse events (nausea) at 24 hours • Hospital readmission	

Study	Intervention and comparison	Population	Outcomes	Comments
	continued to receive oral oxycodone-acetaminophen and ibuprofen. all were discharged with these oral agents. N=46			
Dieterich 2012[56]	**IV PCA:** 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. N=126 **Oral opioid (immediate release):** Patients received 20 mg Oxycodone at fixed intervals at 2 and 12 hours after the CS N=113	Main inclusion criteria were CS in spinal anaesthesia, no history of opioid or metamizol treatment, written consent and ability to use a PCA device. Mean age (SD) PCA – 29.8 Oral – 28.5(5.9) Germany	• Pain score (VAS) at 24 hours	
ONG 2005[172]	**IV (not PCA):** 50-mg/mL injectable ampoules; injectable tramadol was diluted to 2 ml using physiologic saline. An intravenous cannula was	72 patients undergoing elective surgical removal of impacted mandibular third molars in an outpatient setting participated in the	• Pain score (VAS) at 8 hours • Pain score (Global assessment score) at 8 hours	

Study	Intervention and comparison	Population	Outcomes	Comments
	inserted into the antecubital fossa or dorsum of the hand in all patients for the administration of drugs. N=36 **Oral opioid (immediate release):** 50 mg capsules given 15 min preoperatively. N=36	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 Mean age (SD) IV – 25.3 (3.9) Oral – 24.3 (4.3) USA	• Amount of additional medication (Acetaminophen consumption) during first 8 hours	
Rothwell 2011[195]	**IV PCA:** IV morphine boluses from the pump. The IVPCA settings were 1 mg bolus, 5 min lockout time and no loading dose IV PCA patients continued with the PCA until either they wished to discontinue it or they were using 1mg/h^{-1}. N=57 **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.	Patients undergoing THR, age 60–85 yr, ASA health status class I–III, and willing to undergo spinal anaesthesia. Mean age (range) PCA – 71 (60-79) Oral opioid – 72 (60-79) UK	• Pain (NRS at rest) at 24 h • Adverse events (nausea score Mean) at 24 h	

Study	Intervention and comparison	Population	Outcomes	Comments
	N=57			
Ruetzler 201[200]	**PCA**: 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. N=26 **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. N=25	51 patients scheduled for elective conventional on-pump cardiac surgery requiring median sternotomy between July 2011 and May 2012 Mean age (SD) PCA – 63(14) Oral – 67(15) Austria	• Adverse events(Nausea + vomiting) 3 days post operatively	
Striebel 1998[216]	**PCA:** PCIA group (bolus 2.0 mg of morphine, lockout time 12 min, loading dose 2 mg, maximal dose 10 mg/h) N=32). **Oral opioid (Immediate release):** Oral opioid group (maximal dose 20 mg of morphine per 60 min, loading dose 40 mg;) A 4% aqueous morphine solution (40 mg/mL)	At least 1 day before surgery, ASA physical status I or II patients undergoing orthopaedic surgery (17 and 19 internal fixations, and 10 and 7 other procedures (endoprosthesis, arthrodesis, external fixation for PCOA and PCIA Mean age (SD)	• Adverse events day 1	

Study	Intervention and comparison	Population	Outcomes	Comments
	was used for PCOA. N=32).	PCA – 43.7 (15.9) PCOA – 39.9 (13.1) Germany		

3.3.4 Quality assessment of clinical studies included in the evidence review

Table 36: Clinical evidence summary: IV opioid versus oral (immediate release)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Iv opioid versus oral opioid immediate release (95% CI)
Pain (VAS) at >6 h	93 (1 study) 6 hours	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain (vas) at >6 h in the control groups was 3.2	The mean pain (vas) at >6 h in the intervention groups was 0.9 higher (0.02 to 1.78 higher)
Pain (VAS) at 6-24 h	404 (3 studies) 6-24 Hours	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain (vas) at 6-24 h in the control groups was 4.773	The mean pain (vas) at 6-24 h in the intervention groups was 0.88 lower (1.25 to 0.52 lower)
Pain (Global assessment score) 6-24 h	72 (1 study) 8 hours	⨁⨁⨁⊖ MODERATE3 due to indirectness		The mean pain (global assessment score) 6-24 h in the control groups was 1.1	The mean pain (global assessment score) 6-24 h in the intervention groups was 1.5 higher (1.11 to 1.89 higher)
Adverse events (mean) at 6 hours	93 (1 study) 0-6 Hours	⨁⨁⊖⊖ LOW1 due to risk of bias		The mean adverse events (mean) at 6 hours in the control groups was 0.2	The mean adverse events (mean) at 6 hours in the intervention groups was 1.8 higher

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Iv opioid versus oral opioid immediate release (95% CI)
					(0.79 to 2.81 higher)
Adverse events (mean)at 24 hours	93 (1 study) 6-24 Hours	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean adverse events (mean)at 24 hours in the control groups was 1	The mean adverse events (mean)at 24 hours in the intervention groups was 0.7 lower (1.32 to 0.08 lower)
Adverse events	60 (1 study) 1 days	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.33 (0.07 to 1.52)	Moderate	
				200 per 1000	134 fewer per 1000 (from 186 fewer to 104 more)
hospital readmission	93 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Risk difference 0 (-0.04 to 0.04)	Moderate	
				0 per 1000	Not estimable
additional medication (acetaminophen consumption)6-24 h	72 (1 study) 8 hours	⨁⨁⨁⊖ MODERATE2,3 due to indirectness		The mean additional medication (acetaminophen consumption)6-24 h in the control groups was 3.558	The mean additional medication (acetaminophen consumption)6-24 h in the intervention groups was 1.74 lower (2.36 to 1.11 lower)
Amount of additional medication (number of people)	93 (1 study) 24 hours	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.73 (0.17 to 3.1)	Moderate	
				87 per 1000	23 fewer per 1000 (from 72 fewer to 183 more)

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 37: IV opioid versus oral (modified release)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IV opioiod versus oral opioid modified release (95% CI)
Pain (NRS) at 24 hours	110 (1 study) 24 hours	⊕⊕⊖⊖ LOW1,2 due to risk of bias		The mean pain (nrs) at 24 hours in the control groups was 1.65	The mean pain (nrs) at 24 hours in the intervention groups was 0.08 higher (0.77 lower to 0.93 higher)
Adverse events (Mean Nausea score)	110 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean adverse events (mean nausea score) in the control groups was 0.59	The mean adverse events (mean nausea score) in the intervention groups was 0.11 higher (0.38 lower to 0.6 higher)
Adverse Events (Nausea, Vomiting)	50 (1 study) 3 days	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.27 (0.62 to 2.61)	Moderate	
				333 per 1000	90 more per 1000 (from 127 fewer to 536 more)

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 38: Evidence not suitable for GRADE analysis: IV opioid versus Oral (Immediate release)

Outcome	Study (no. of participants)	Risk of bias	Comparison (oral opioid) results	Intervention (IV opioid) results	*P* value
Amount of additional medication used	Dieterich 2012 (239)	Very high	Reported on a graph only Proportion of patients that did	Reported on a graph only Proportion of patients that did	n/a

Outcome	Study (no. of participants)	Risk of bias	Comparison (oral opioid) results	Intervention (IV opioid) results	*P* value
			not need the additional medication on day 1: Oxycodone group ~51 % 1-2 dispenses of additional medication needed on day 1 Oxycodone ~32% 3 dispenses of additional medication needed on day 1 Oxycodone ~11% Proportion of patients that did not need the additional medication on day 2: Oxycodone group ~76 % 1-2 dispenses of additional medication needed on day 2 Oxycodone ~18% 3 dispenses of additional medication needed on day 2 Oxycodone ~4%	not need the additional medication on day 1: PCA ~45% 1-2 dispenses of additional medication needed on day 1 PCA~38% 3 dispenses of additional medication needed on day 1 PCA~12% Proportion of patients that did not need the additional medication on day 2: PCA ~72% 1-2 dispenses of additional medication needed on day 2 PCA~12% 3 dispenses of additional medication needed on day 2 PCA~10%	
Length of hospital stay	Dieterich 2012 (239)	Very high	Reported as overall mean – 4.2 days	Reported as overall mean – 4.2 days	n/a

Outcome	Study (no. of participants)	Risk of bias	Comparison (oral opioid) results	Intervention (IV opioid) results	*P* value
Pain score (VAS)	Striebel 2012 (60)	Very high	Reported on graph only ~2 at hour 8 post operatively	Reported on a graph only ~2.1 at hour 8 post operatively	n/a

Table 39: Evidence not suitable for GRADE analysis: IV opioid compared to Oral opioid (modified release)

Outcome	Study (no. of participants)	Risk of bias	Comparison (oral opioid) results	Intervention (IV opioid) results	*P* value
Pain score (VAS)	Ruetzler 2014 (51)	Very high	Adjusted difference of means oral vs IV (98.7% CI) 3.4 (-4.3; 11.2)		n/a
Length of stay at ICU	Ruetzler 2014 (51)	Very high	Median (range): 1 day (1,2) for both groups		n/a
Length of hospital stay	Ruetzler 2014 (51)	Very high	Median (range): 8.5 days (8,12)	Median (range): 9 days (8,11)	n/a

See appendices for full GRADE tables.

3.4 Economic evidence

3.4.1 Included studies

No health economic studies were included.

3.4.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendices.

3.4.3 Unit costs

The average daily costs of intravenous and oral opioids are provided in Table 40 to help aid consideration of cost effectiveness. A breakdown of these costs is provided in the appendices for the pain evidence review.

Table 40: Average daily costs of intravenous opioid and intravenous paracetamol

Analgesic	Average daily cost per person (range)
Oral opioid	£0.24 (£0.02 - £0.63)
Intravenous opioid	£4.92 (£3.77 – £6.07)[(a)]
Patient controlled analgesia (opioid)	£21.10 (£16.36 - £23.79)[(a)]

Sources: British National Formulary, Accessed September 2019[101]; Electronic market information tool (eMIT), Accessed September 2019[43]

(a) Costs include disposable costs, see the appendices for the pain evidence review for a breakdown of these costs.

Evidence statements

3.4.4 Clinical evidence statements

No outcomes were reported for health related quality of life or the following important outcomes; psychological distress and mental well-being, symptom scores and functional measures.

IV opioid versus oral (immediate release)

Pain relief

One study found no clinically important difference in pain within 6 hours of surgery between IV and oral opioid (1 study, n=93, very low quality evidence).

Three studies showed no clinically important difference between IV and oral opioid in pain at 6 to 24 hours of surgery (3 studies, n=404, very low quality evidence).

One study found a clinically important harm with IV opioid in global pain score at 6 to 24 hours of surgery compared to oral opioid (1 study, n=82, moderate quality evidence).

One study found no clinically important difference between IV and oral opioid in additional medication (acetaminophen) consumption (1 study, n=72, moderate quality evidence).

One study found no clinically important difference between IV and oral opioid in the number of people requesting rescue medication (1 study, n=93, very low quality evidence)

Adverse events

One study found a clinically important harm with IV opioid in mean cases of adverse events within 6 hours of surgery compared to oral opioid (n=93, low quality evidence),

One study found no clinically important difference between IV and oral opioid for mean cases of adverse events from 6 to 24 hours postoperatively (1 study, n=93, very low quality evidence).

One study found a clinically important benefit with IV opioid in cases of adverse events compared to oral opioid (1 study, n=60, very low quality evidence).

Hospital admission

One study found no clinically important difference between IV and oral opioid in hospital readmissions (1 study, n=93, very low quality evidence).

One study found no clinically important difference in additional medication (n=93, very low quality evidene).

Outcome not suitable for GRADE anaylysis

One study showed no notable difference between IV and oral opioid in the amount of in additional medication required (1 study, n=239, very high risk of bias)

One study showed no notable difference between IV and oral opioid in length of hospital stay (1 study, n=239, very high risk of bias)

One study showed no notable difference between IV and oral opioid in pain score (1 study, n=60, very high risk of bias)

IV opioid versus oral (modified release)

One study found no clinically important difference between IV and oral opioid in pain within 24 hours of surgery (1 study, n=110, low quality evidene).

One study found no clinically important difference between IV and oral opioid in mean nausea score (1 study, n=110, very low quality evidene).

One study found no clinically important difference between IV and oral opioid in cases of nausea or vomiting (1 study, n=50, very low quality evidene).

Outcome not suitable for GRADE analysis

One study reported no notable difference between IV and oral opioid in pain scores (1 study, n=51, very high risk of bias)

One study reported no notable difference between IV and oral opioid in length of ICU stay (1 study, n=51, very high risk of bias)

One study reported no notable difference between IV and oral opioid in length of hospital stay (1 study, n=51, very high risk of bias)

3.4.5 Health economic evidence statements

- No relevant economic evaluations were identified.

3.5 Review question 2: What is the most clinically and cost effective opioid administration strategy?

3.6 PICO table

For full details see the review protocol in appendices.

Table 41: PICO characteristics of review question

Population	Adults (18 years and older) who have undergone surgery.
Interventions	• Interventions: • IV PCA (morphine, fentanyl, oxycodone) • Spinal opioid – one administration(diamporphine or/morphine +/- bupivacaine/ levobupivacaine • Continuous epidural (Fentanyl + Bupivacaine, Morphine + Bupivacaine)
Comparisons	• To each other

Outcomes	CRITICAL:
	• health-related quality of life
	• pain reduction
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• amount of additional medication use
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• adverse events (including respiratory depression, nausea, vomiting)
	IMPORTANT:
	• psychological distress and mental well-being
	• symptom scores
	• functional measures
	• length of stay in intensive care
	• length of stay in hospital
	• hospital readmission

Study design	Randomised controlled trials and systematic reviews of randomised controlled trials.

3.7 Clinical evidence

3.7.1 Included studies

Twenty five randomised controlled trials were included in the review; [18, 26, 27, 30, 34, 75, 89, 94, 114, 130, 132, 160, 174, 184, 190, 191, 198, 205, 215, 226, 229, 231, 247, 252, 258] these are summarised in table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See appendices for the study selection flow chart, study evidence tables, forest plots and GRADE tables.

3.7.2 Excluded studies

See the excluded studies list in appendices.

3.7.3 Summary of clinical studies included in the evidence review

Table 42: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Azad 2000[18]	**PCA:** 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 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. N=25 **Continuous epidural:** Patients received a 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. N=25	In all patients thoracotomy was performed for lobectomy, resection of lung tissue or transthoracalmediastinotomy. Age range: 31 – 75 years Germany	• Pain • Complications: ○ Nausea and vomiting • Length of stay	
Benzon 1993[26]	**PCA:** Patients in the PCA group were given morphine through PCA device, 1mL per demand dose.	Patients who were scheduled to undergo thoracotomy and who presented with no contraindication or objection to	• Pain relief • Complications: ○ Nausea	

Study	Intervention and comparison	Population	Outcomes	Comments
	N=18 **Continuous epidural:** Patients in the Epidural group received fentanyl in the epidural infusion and saline through the PCA machine. 5ml/hour. N=18	epidural postoperative analgesia were enrolled after verbal and written informed consent. Mean age (SD): PCA: 60.1 (10.7) Epidural: 56.4 (12.1) USA	○ Vomiting	
Bialka 2018[27]	**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. N=35 **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.	Patients aged between 18 and 77 years with ASA physical status between 1 and 3. Mean age (SD): 63 years (10) Poland	• Pain	PCA groups combined.

Study	Intervention and comparison	Population	Outcomes	Comments
	N=35 **Continuous epidural:** A continuous epidural infusion consisting of 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. N=35			

Boylan 1998[30]	**PCA:** 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.
	N=21
	
	Continuous epidural: 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
		ASA I or II patients undergoing elective infrarenal aortic aneurysm repair or aortobifemoral bypass grafting.
		
		Mean age (SD): 69 years (8.8)
		
		Canada
			• Complications:
			  ○ Nausea
			  ○ Vomiting
			• Length of stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	of epidural 0.25% Bupivacaine and 0.05mf/kg morphine followed by an increase in the infusion rate by an increment of 2ml/h. N=19			
Carli 2002[34]	**PCA:** 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. N=32 **Continuous:** 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. N=32	Adult patients undergoing elective colorectal surgery for nonmetastatic conditions Mean age (SD): Epidural 59 years (12) PCA 62 years (12) USA	• Pain • Functional score • Length of hospital stay • Hospital readmission	
George1994[75]	**PCA:** Morphine was given by one of the investigators at 1mg per min intravenously to maximum of 20 mg or until	Adult patients, ASA status I or II in the age range 20-74 years and undergoing upper abdominal surgery	• Pain • Complications: ○ Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	patient was comfortable. The PCA device was the activated. N=11 **Continuous**: 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. N=10	Mean age (SD): Epidural 43(14) PCA 44 (21).		
Hausken 2019[89]	**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. N= 66 **Continuous:** Thoracic epidural – consisted 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. N= 77	143 patients operated with open liver resection between Feb 2012- Feb 2016 within an enhanced recovery programme. Age range 62.8 – 69.3 Norway	• Pain • ICU stay • Length of hospital stay • Complications – nausea and vomiting • Readmission within 30 days • Additional medication use	Surgeons, nurses, patients all un-blinded
Hubner 2015[94]	**PCA:** I.V 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	Patients undergoing laparoscopic colorectal surgery Mean age (SD):	• Mortality • Length of hospital stay • Length of stay in HDU	

Study	Intervention and comparison	Population	Outcomes	Comments
	N=61 **Continuous:** 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) N=67	PCA: 61.2 years (17.8) Epidural: 63.1 years (15.1) Switzerland	• Readmission	
Kjolhede 2019[114]	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. N = 40 Epidural (EDA) - 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	Eighty women patients, 18–70 years of age, ASA grade I and II, admitted consecutively to the department of Obstetrics and Gynaecology in an ERAS programme after midline laparotomy for proven or assumed gynaecological malignancies. Sweden	• Pain • Length of stay • QOL • Consumption of additional medication	Comments Epidural + additional PCA For the EDA group 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.

Study	Intervention and comparison	Population	Outcomes	Comments
	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. N= 40			
Liu 1995[130]	**PCA:** Received 5mg morphine intravenously after induction of GA. PCA morphoine 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. N=12 **Continuous:** 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. N=12	Patients scheduled to undergo partial resection of the colon. Mean age (SE): 62.5 years (1) USA	• Pain • Complications: ○ Nausea	
Madej 1992[132]	**PCA:** Self-administered i.v. diamorphine at a maximum	Patients scheduled to undergo total abdominal hysterectomy.	• Pain	

Study	Intervention and comparison	Population	Outcomes	Comments
	rate of 1 mg every 5 min using a Graseby Patient Controlled Analgesia System. N=10 **Continuous:** Received an extradural infusion of 0.15% bupivacaine with 0.01% diamorphine 4-6 ml/h^{-1}. N=20	Mean age (SD): 58.4 years (14.6) UK	• Complications: ○ Vomiting	
Motamed 1998[160]	**PCA:** Intravenous morphine (1 mg bolus, 5-min lock-out and maximum dose 20 mg 4h-1). N=30 **Continuous:** An extradural infusion of 0.125% bupivacaine with morphine 0.25 mg/ml-1 was given at the rate of 10 ml/h-1. N=30	Patients ASA I or II aged 18-70 years, due to undergo major abdominal surgery for cancer (midline or bisubcostal incision). Mean age (SD): 58 years (10) France	• Pain • Additional medication use	No supplementary analgesic was given during the first 48 h; if this was needed, the patient was withdrawn from the study.
Owen 1993[174]	**PCA:** Fentanyl bolus dose 25 ug with a 15 min lockout interval from a PCA pump. N=12 **Continuous:** Fentanyl 50ug/h^{-1} (10ug/ml^{-1}) along with nurse-administered fentanyl boluses of 25ug. N=15	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. Mean age (SD): 54 years (15) Australia	• Pain	
Paulsen 2001[184]	**PCA:** Morphine was used at a dose of mg IV every 10	Men or women ages ≥18 who were scheduled to undergo an	• Pain	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. N=25 **Continuous:** 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. N=24	elective small bowel or colon resection with a primary anastomosis. Mean age (SD): PCA 65.1 years (12.2) Epidural 61.3 years (13.4) USA	• Length of hospital stay	
Radovanovic 2017[190]	**PCA:** 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	ASA physical status I-III, signed informed consent to participate in the study, and elective open colorectal cancer surgery performed. Mean age (SD): PCA: 64.18years (9.90) Epidural: 65.88 years (10.00)	• Length of hospital stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	persisted, the bolus dose was increased in 0.5mg increments every second hour. N=30 **Continuous:** 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 N=30	Serbia		
Rauck 1994[191]	**PCA:** 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. N=15 **Continuous:** 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	ASA status I-III patients undergoing upper abdominal surgery. Mean age (range): 44 years (18-79) USA	• Pain • Complications: ○ Nausea and vomiting • Length of stay	Different doses of morphine given at surgery close.

Study	Intervention and comparison	Population	Outcomes	Comments
	maintain adequate pain relief and minimise side effects. N=15			
Royse 2003[198]	**PCA:** Patient controlled intravenous morphine (1 mg bolus with 5 minute lockout period), which was continued until 6:00 am on postoperative day 3. N=40 **Continuous:** 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 N=40	Patients undergoing Coronary artery bypass graft. Mean age (SD): Epidural: 64.2 years (9.3) PCA: 65.1 years (10.8) Australia	• Pain • Depression • Psychological distress and mental well-being • Length of hospital stay • ICU length of stay	
Senturk 2002[205]	**PCA:** 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. N=28 **Continuous:**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. N=29	ASA status II–III patients undergoing thoracotomy. Mean age (SD): PCA: 50 years (11) Epidural: 50.57 years (10.2) Turkey	• Pain	

Study	Intervention and comparison	Population	Outcomes	Comments

Steinberg 2002[215]	**PCA:** 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.
	N=21
	
	Continuous: 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
		ASA < IV; 18 - 80 years of age; weight 50 - 110kg.
		
		Mean age (SD):
		PCA: 61 years (15)
		Epidural: 61 years (10)
		
		USA
			• Length of hospital stay
			• Complications:
			  ○ Nausea
			  ○ Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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.			

Study	Intervention and comparison	Population	Outcomes	Comments
	N=20			

Taqi 2007[226]	**PCA:** 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.
	N=25
	
	Continuous: 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.
	N=25
		Scheduled to undergo elective laparoscopic colorectal surgery for benign and malignant colorectal lesions
		
		Mean age (SD):
		PCA: 61.24 years (14.91)
		Epidural: 65 years (16.18)
		
		Canada
			• Pain
			• Length of hospital stay
			• Readmission
			• Complications:
			  ○ Nausea
			  ○ Vomiting	

Tenenbein 2008[229]	**PCA:** 1.0mg iv boluses with a five-minute lockout for 48 hr N=25 **Continuous:** 0.2% ropivacaine, with 15 µg·mL–1 of hydromorphone N=25	Patients less than 80 yr of age, who were deemed appropriate for the facilitated recovery program. Mean age (SD): PCA: 60.8 years (9.4) Epidural: 60.1 years (6.3) Canada	• Pain	

Tsui 1997[231]	**PCA:** Patients received incremental IV boluses of morphine 1mg every 5 minutes	ASA I or II female patients scheduled for gynecological lower abdominal operations	• Complications:
			  ○ Nausea
			  ○ Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. N=54 **Continuous:** 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. N=57	through a vertical midline incision. Mean age (SD): PCA: 48 years (11) Epidural: 51 years (16) Hong Kong (China)	○ Respiratory depression	
Wheatley 1990[247]	**PCA:** Patients self-administered i.v. diamorphine at a maximum rate of 1 mg every 20 min, commenced within 1 hour of surgery N=10 **Continuous:** Extradural diamorphine in doses of 3.6 mg in saline 9 ml administered by the anaesthetist or senior nursing staff as requested by the patient. This was repeated	Patients scheduled for general anaesthesia and lower abdominal surgery Mean age (range): PCA: 40.2 years (28-51) Extradural 43.2 years (35-52) UK	• Pain • Complications: ○ Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	as necessary during the 24 hour period. N=10			

Wongyingsinn 2012[252]	**Spinal:** 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
	N=25
	
	PCA: 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)
	N=25
		All patients undergoing elective laparoscopic colon resection and >18 yr were enrolled in the study.
		
		Median age (IQR):
		Spinal: 65 years (39-85)
		PCA: 65 years (34-83)
		
		Canada
			• Pain
			• Length of hospital stay
			• Readmission
			• Complications:
			  ○ Nausea
			  ○ Vomiting
			  ○ Respiratory depression	

Zejun 2018[258]	**PCA:** 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.
	N=50
	
	Continuous: 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.
		Patients qualified for VATS lobectomy as a result of cancer; aged 18–70 years; of either gender; and ASA status I–III.
		
		Mean age (SD):
		PCA: 54.9 years (11.7)
		Epidural: 57.8 years (8.1)
		
		China
			• Length of hospital stay
			• Complications:
			  ○ Nausea
			  ○ Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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). N=49			

See appendices for full evidence tables.

3.7.4 Quality assessment of clinical studies included in the evidence review

Table 43: Clinical evidence summary: PCA compared to continuous epidural for post-operative pain management

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuous epidural	Risk difference with PCA (95% CI)
Pain: VAS (6 hours) Scale from: 0 to 10.	272 (5 studies)	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain: vas (6 hours) in the control groups was 2.11	The mean pain: vas (6 hours) in the intervention groups was 1.51 higher (0.66 to 2.36 higher)
Pain: VAS (12 hours) Scale from: 0 to 10.	164 (3 studies)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean pain: vas (12 hours) in the control groups was 1.7	The mean pain: vas (12 hours) in the intervention groups was 0.96 higher (0.52 to 1.4 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuous epidural	Risk difference with PCA (95% CI)
Pain: VAS (24 hours) Scale from: 0 to 10.	726 (8 studies)	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain: vas (24 hours) in the control groups was 0.96	The mean pain: vas (24 hours) in the intervention groups was 1.33 higher (0.60 to 2.05 higher)
Pain: VAS (48 hours) Scale from: 0 to 10.	654 (7 studies)	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain: vas (48 hours) in the control groups was 0.57	The mean pain: vas (48 hours) in the intervention groups was 1.26 higher (0.68 to 1.83 higher)
Pain relief: TOTPAR (24 hours)	34 (1 study)	⨁⨁⨁⨁ HIGH		The mean pain relief: totpar (24 hours) in the control groups was 14.7	The mean pain relief: totpar (24 hours) in the intervention groups was 1.9 lower (2.94 to 0.86 lower)
Pain relief: TOTPAR (48 hours)	34 (1 study)	⨁⨁⨁⊖ MODERATE1 due to imprecision		The mean pain relief: totpar (48 hours) in the control groups was 16.2	The mean pain relief: totpar (48 hours) in the intervention groups was 2.8 lower (4.3 to 1.3 lower)
Total medication (Morphine)	57 (1 study) 2 days	⨁⨁⨁⊖ MODERATE2 due to risk of bias		The mean total medication (morphine) in the control groups was 11.9 mg	The mean total medication (morphine) in the intervention groups was 53.9 higher (47.43 to 60.37 higher)
Depression	52 (1 study) 6 weeks	⨁⨁⨁⊖ MODERATE2 due to risk of bias	RR 1.59 (0.44 to 5.67)	Moderate	
				130 per 1000	77 more per 1000 (from 73 fewer to 607 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuous epidural	Risk difference with PCA (95% CI)
Post-traumatic Stress	52 (1 study) 6 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 2.94 (0.85 to 10.13)	Moderate	
				103 per 1000	200 more per 1000 (from 15 fewer to 940 more)
Complication - Nausea	380 (6 studies) post-operative period	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, inconsistency, imprecision	RR 0.99 (0.58 to 1.7)	Moderate	
				328 per 1000	3 fewer per 1000 (from 138 fewer to 230 more)
Complication - Vomiting	371 (7 studies) post-operative period	⨁⨁⊖⊖ LOW1,2,3 due to risk of bias, inconsistency	RR 2.15 (1.03 to 4.46)	Moderate	
				168 per 1000	193 more per 1000 (from 5 more to 581 more)
Complication - nausea and vomiting	223 (3 studies) post-operative period	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, imprecision	RR 1.06 (0.63 to 1.77)	Moderate	
				205 per 1000	12 more per 1000 (from 76 fewer to 158 more)
Complication - Respiratory depression	111 (1 study) post-operative period	⨁⨁⨁⊖ MODERATE2 due to risk of bias	RD 0 (-0.03 to 0.03)	Moderate	
				0 per 1000	Not estimable
Functional measures - Distance walked in 6 minutes	64 (1 study) 3 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean functional measures - distance walked in 6 minutes in the control groups was -32 meters	The mean functional measures - distance walked in 6 minutes in the intervention groups was 30.9 lower (64.62 lower to 2.82 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuous epidural	Risk difference with PCA (95% CI)
Functional measures - Distance walked in 6 minutes	64 (1 study) 6 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean functional measures - distance walked in 6 minutes in the control groups was -5 meters	The mean functional measures - distance walked in 6 minutes in the intervention groups was 16.7 lower (43.12 lower to 9.72 higher)
Length of stay	324 (4 studies)	⨁⨁⨁⊖ MODERATE2 due to risk of bias		The mean length of stay in the control groups was 7.37 days	The mean length of stay in the intervention groups was 0 higher (0.5 lower to 0.5 higher)
ICU length of stay	76 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean icu length of stay in the control groups was 45.6 hours	The mean icu length of stay in the intervention groups was 2.5 higher (3.92 lower to 8.92 higher)
Hospital readmission	379 (4 studies) discharge to 30 days	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.57 (0.26 to 1.27)	Moderate	
				80 per 1000	34 fewer per 1000 (from 59 fewer to 22 more)

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 44: Clinical evidence summary: PCA compared to spinal epidural for post-operative pain management

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Spinal epidural	Risk difference with PCA (95% CI)
Readmission	49 (1 study) 30 days	⨁⨁⨀⨀ LOW1 due to imprecision	RR 1.04 (0.07 to 15.73)	Moderate	
				40 per 1000	2 more per 1000 (from 37 fewer to 589 more)
Complication - Nausea	49 (1 study)	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.87 (0.3 to 2.47)	Moderate	
				240 per 1000	31 fewer per 1000 (from 168 fewer to 353 more)
Complication - Vomiting	49 (1 study)	⨁⨁⨀⨀ LOW1 due to imprecision	RR 1.04 (0.34 to 3.15)	Moderate	
				200 per 1000	8 more per 1000 (from 132 fewer to 430 more)
Complication - Respiratory depression	49 (1 study)	⨁⨁⨀⨀ LOW1 due to imprecision	Peto OR 7.7 (0.15 to 388.55)	Moderate	
				0 per 1000	Not estimable
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 45: Clinical evidence summary: Spinal epidural compared to continuous for post-operative pain management

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuous epidural	Risk difference with spinal epidural (95% CI)
Complications (clavien dindo grade I)	80 (1 study) 6 weeks	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.62 (0.29 to 1.32)	Moderate	
				325 per 1000	123 fewer per 1000 (from 231 fewer to 104 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuous epidural	Risk difference with spinal epidural (95% CI)
Complications (clavien dindo grade II)	80 (1 study) 6 weeks	⨁⨁⊖⊖ LOW1 due to imprecision	RR 1 (0.35 to 2.84)	Moderate	
				150 per 1000	0 fewer per 1000 (from 98 fewer to 276 more)
Complications (clavien dindo grade III)	80 (1 study) 6 weeks	⨁⨁⊖⊖ LOW1 due to imprecision	RR 6 (0.76 to 47.6)	Moderate	
				25 per 1000	125 more per 1000 (from 6 fewer to 1000 more)
Complications (clavien dindo grade IV)	80 (1 study) 6 weeks	⨁⨁⊖⊖ LOW1 due to imprecision	RR 1 (0.06 to 15.44)	Moderate	
				25 per 1000	0 fewer per 1000 (from 24 fewer to 361 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 46: Evidence not suitable for GRADE analysis: PCA compared to continuous epidural for post-operative pain management

Outcome	Study (no. of participants)	Risk of bias	Comparison (continuous) results	Intervention (PCA) results	*P* value
Pain (VAS): <6 hours	Motamed 1998[160](60)	High	VAS scores were significantly lower at 2h postoperatively in the continuous epidural group at rest and while coughing.		<0.05

Outcome	Study (no. of participants)	Risk of bias	Comparison (continuous) results	Intervention (PCA) results	*P* value
	George 1994[75](21)	High	Median (range) at 2 hours: ~0 (0-5)	Median (range) at 2 hours: ~6 (1.5-9)	n/a
	Madej 1992[132](50)	High	Pain scores at 4 hours post-operation showed no significant difference with continuous epidural morphine and bupivacaine and PCA diamorphine.		>0.05
	George 1994[75](21)	High	Median (range) at 6 hours: ~0 (0-2.5)	Median (range) at 6 hours: ~4 (0.2-6.5)	n/a
Pain (VAS): day 1	George 1994[75](21)	High	Median (range) at 18 hours: ~2 (0-2.2)	Median (range) at 18 hours: ~2.1 (0-9)	n/a
	George 1994[75](21)	High	Median (range) at 24 hours: ~1 (0-2)	Median (range) at 24 hours: ~1.8 (0-7)	n/a
	Madej 1992[132](50)	High	Pain scores at 12-24 hours post-operation were significantly lower with continuous epidural morphine and bupivacaine compared to PCA diamorphine.		<0.05
	Motamed 1998[160](60)	High	VAS scores were significantly lower at 8 and 24 h postoperatively in the continuous epidural group at rest and while coughing.		<0.05
	Liu 1995[130](54)	High	Pain scores with morning ambulation were significantly lower with continuous epidural morphine and bupivacaine on day 1.		<0.01
	Paulsen 2001[184](49)	High	Median (IQR): 1.8 (0.5-4.7)	Median (IQR): 3.9 (2.7-4.7)	n/a

Outcome	Study (no. of participants)	Risk of bias	Comparison (continuous) results	Intervention (PCA) results	*P* value
	Taqi 2007[226](50)	High	Median (IQR): 1 (0.80 – 2.09)	Median (IQR): 4 (2.74 – 5.02)	n/a
Pain (VAS): day 2	Paulsen 2001[184](49)	High	Median (IQR): 1.7 (0.2-3.3)	Median (IQR): 4.2 (2.4-4.8)	n/a
	Taqi 2007[226](50)	High	Median (IQR): 0 (0.39 – 1.54)	Median (IQR): 3 (1.98 – 4.18)	n/a
	Liu 1995[130](54)	High	Pain scores with morning ambulation were significantly lower with continuous epidural morphine and bupivacaine.		<0.01
Pain (VAS): total pain days 0 to 5	Hausken 2019[89] (143)	Very high	Mean: 1.6 (no SD data provided)	Mean: 1.7 (no SD data provided)	n/a
Complications: nausea	Benzon 1993[26](36)	Low	Mild nausea experienced by 30 - 50 % in both groups		n/a
	Liu 1995[130] (24)	Low	8/12	14/12	n/a
Length of stay	Boylan 1998[30](40)	High	Median (IQR): 13 days (10-17)	Median (IQR): 14 days (13-15)	n/a
	Zejun 2018[258](99)	High	Median (IQR): 5.0 days (3.5-7.0)	Median (IQR): 5.0 days (4.0-8.5)	0.94
	Hubner 2015[94](128)	Low	Median (IQR): 7 days (4.5-12)	Median (IQR): 5 days (4-8)	0.43

Outcome	Study (no. of participants)	Risk of bias	Comparison (continuous) results	Intervention (PCA) results	*P* value
	Steinberg 2002[215](48)	High	Median (IQR): 5.0 days (2.0 - 18.7)	Median (IQR): 4.8 days (3.8 - 30.0)	n/a
	Hausken 2019[89] (143)	Low	Median (IQR) 4 days (3.25-6.41)	Median (IQR) 3 days (2.13-4.5)	n/a
	Taqi 2007[226](50)	High	Median (IQR): 5 days (4.65 - 6.16)	Median (IQR): 5 days (4.23 - 9.53)	n/a
ICU/HDU Length of stay in	Hubner 2015[94](128)	Low	Median (IQR): 1 day (1-2.5)	Median (IQR): 1 day (0-1)	0.213
	Boylan 1998[30](40)	High	Median (IQR): 2 days (1 - 2)	Median (IQR): 2 days (2 - 2)	n/a
	Hausken 2019[89] (143)	Low	Median (IQR): 230 minutes (45 - 1834)	Median (IQR): 275 minutes (108 - 1858)	n/a
Use of additional opoids days 0 to 2	Hausken 2019[89] (143)	Very high	The consumption of morphine equivalents were significantly lower and the decline in morphine consumption was more rapid in the PCA group compared to the epidural.		n/a

Table 47: Evidence not suitable for GRADE analysis: PCA compared to spinal epidural for post-operative pain management

Outcome	Study (no. of participants)	Risk of bias	Comparison (spinal) results	Intervention (PCA) results	*P* value
Pain (VAS): day 1	Wongyingsinn 2012[252](50)	High	Median (IQR): 0 (0-1.5)	Median (IQR): 2 (1-4)	0.004

Outcome	Study (no. of participants)	Risk of bias	Comparison (spinal) results	Intervention (PCA) results	*P* value
Pain (VAS): day 2	Wongyingsinn 2012[252](50)	High	Median (IQR): 0 (0-2)	Median (IQR): 1 (0-4)	0.15
Length of stay	Wongyingsinn 2012[252](50)	High	Median (IQR): 3 (3-4)	Median (IQR): PCA: 3 (3-4)	0.59

Table 48: Evidence not suitable for GRADE analysis: Spinal epidural compared to continuous epidural for post-operative pain management

Outcome	Study (no. of participants)	Risk of bias	Comparison (continuous epidural) results	Intervention (spinal epidural) results	*P* value
Overall assessment of pain: 0-6 days	Kjolhede 2019[114] (80)	Very high	There was no significant difference in the overall assessment of pain at rest between the two groups in 0 to 6 days post operatively (p 0.34).		0.34
Length of stay	Kjolhede 2019[114] (80)	Low	Median (IQR): 4.3 days (3.4-5.2)	Median (IQR): 3.3 (3.1-4.8)	0.01
ICU length of stay	Kjolhede 2019[114] (80)	Low	Median (IQR): 5.7 days (4.0-8.1)	Median (IQR): 4.6 (4.2- 5.6)	n/a
Total consumption of opioids day 0 to 6 (morphine equivalent)	Kjolhede 2019[114] (80)	High	Median (IQR): 81mg (67-101)	Median (IQR): 20mg (14-35)	<0.0001
QOL (SF-36) Physical component score at 6 weeks post-op	Kjolhede 2019[114] (80)	High	Median (IQR): 39 (34-44)	Median (IQR): 38 (35-42)	0.41

Outcome	Study (no. of participants)	Risk of bias	Comparison (continuous epidural) results	Intervention (spinal epidural) results	*P* value
QOL (SF-36) Mental component score at 6 weeks post-op	Kjolhede 2019[114] (80)	High	Median (IQR): 49 (34-53)	Median (IQR): 51 (39-55)	0.05
QOL (EQ-5D)	Kjolhede 2019[114] (80)	High	QOL measured by the EQ-5D, day by day, presented no statistically significant differences in health index between the 2 groups (P= 0.22).		0.22

See appendices for full GRADE tables.

3.8 Economic evidence

3.8.1 Included studies

No health economic studies were included.

3.8.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in the appendices.

3.8.3 Unit costs

The average daily costs of epidural and patient-controlled analgesia are provided inTable 49 to help aid consideration of cost effectiveness. A breakdown of these costs is provided in the appendices for the pain evidence review.

Table 49: Average daily costs of epidurals and patient-controlled analgesia

Analgesic	Average daily cost per person (range)[(a)]
Spinal epidural	£12.45 (£11.06 - £13.83)
Continuous epidural	£27.97
Patient controlled analgesia (opioid)	£21.10 (£16.36 - £23.79)

Sources: British National Formulary, Accessed September 2019[101]; Electronic market information tool (eMIT), Accessed September 2019[43]

(a) Costs include disposable costs, see the appendices for the pain evidence review for a breakdown of these costs.

3.9 Evidence statements

3.9.1 Clinical evidence statements

No outcomes were reported on symptom scores.

PCA compared to continuous epidural pain management

Pain relief

Five studies showed a clinical harm with PCA for pain six hours post-surgery compared to continuous epidural (5 studies, n=272, very low quality evidence)

Three studies showed no clinically important difference between PCA and continuous epuidural in pain at twelve hours postoperatively (3 studies, n=164, low quality evidence)

Eight studies showed a clinical harm with PCA for pain twenty four hours postoperatively compared to continuous epidural (8 studies, n=726, very low quality evidence)

Seven studies showed a clinical harm with PCA for pain forty eight hours postoperatively compared to continuous epidural (7 studies, n=654, very low quality evidence)

One study showed a clinically important harm with PCA in total pain relief at twenty four hours compared to continuous epidural (1 study, n=34, high quality evidence)

One study showed a clinically important harm with PCA in total pain relief at forty eight hours compared to continuous epidural (1 study, n=48, moderate quality evidence)

Rescue medication

One study showed a clinically important harm with PCA in morphine consumption compared to continuous epidural (1 study, n=52, moderate quality evidence)

One study showed no clinically important difference between PCA and continuous epidural rates of depression (1 study, n=52, moderate quality evidence)

Adverse events

One study showed a clinically important harm with PCA in post-traumatic stress compared to continuous epidural (1 study, n=52, low quality evidence)

Six studies showed no clinically important difference between PCA and continuous epidural for the occurrence of nausea (6 studies, n=380, very low quality evidence)

Seven studies showed a clinically important harm with PCA in cases of vomiting compared to continuous epidural (7 studies, n=371, low quality evidence)

Three studies showed no clinically important difference between PCA and continuous epidural for the occurrence of nausea and vomiting (3 studies, n=223, very low quality evidence)

One study showed a clinically important benefit with PCA in cases of daily nausea compared to continuous epidural (1 study, n=24, low quality evidence)

One study showed no clinically important difference between PCA and continuous epidural for the occurrence of respiratory depression (1 study, n=111, moderate quality evidence)

Functional measure

One study showed no clinically important difference between PCA and continuous epidural in distance walked in 6 minutes at 3 or 6 weeks (1 study, n=64, moderate quality evidence)

Length of stay

Four studies showed no clinically important difference between PCA and continuous epidural in length of hospital stay (4 studies, n=324, moderate quality evidence)

One study showed no clinically important difference between PCA and continuous epidural in length of ICU stay (1 study, n=76, low quality evidence)

Hospital readmission

Four studies showed no clinical difference in hospital readmissions (4 studies, n=379, very low quality evidence)

Evidence not suitable for GRADE analysis

Pain relief

One study showed a stastically significant benefit with continuous epidural for pain scores under six hours postoperatively compared to PCA (1 study, n=60, high risk of bias)

One study showed no stastically significant difference between continuous epidural and PCA for pain scores under six hours postoperatively (1 study, n=50, high risk of bias)

One study showed a trend to benefit with continuous epidural for pain scores at two hours and six hours postoperatively compared to PCA (1 study, n=21, high risk of bias)

Three studies showed a trend to benefit with continuous epidural for pain scores on postoperative day 1 compared to PCA (3 studies, n=120, high risk of bias)

Three studies showed a statistically significant difference with continuous epidural in pain scores on postoperative day one compared to PCA (3 studies, n=164, high risk of bias)

Two studies showed a trend towards benefit with continuous epidural for pain scores forty eight hours postoperatively compared to PCA (2 studies, n=99, high risk of bias)

One study showed a statistically significant benefit with continuous epidural for pain scores on the second postoperative day (1 study, n=54, high risk of bias)

One study showed no notable difference between continuous epidural and PCA for pain scores from postoperatively up to day five (1 study, n=143, very high risk of bias)

Rescue medication

One study showed a notable difference with PCA in the amount of additional opioids used postoperatively up to day two (1 study, n=143, very high risk of bias)

Adverse events

Two studies showed no notable difference between PCA and continuous epidural in rates of nausea postoperatively (2 studies, n=60, low risk of bias)

Length of stay

Four studies showed no notable difference between PCA and continuous epidural in length of stay (4 studies, n=281, high risk of bias)Two studies showed no statistically significant difference between continuous epidural and PCA for length of stay (2 studies, n=227, high risk of bias)

Two studies showed no notable difference between PCA and continuous epidural in length of stay in ICU (2 studies, n=183, high risk of bias)One study showed no statistically significant difference between PCA and continuous epidural in length of ICU stay (1 study, n= 128, low risk of bias)

PCA compared to spinal epidural for pain management

Hospital readmission

One study showed no clinically important difference between PCA and spinal epidural in hospital readmissions (1 study, n=49, low quality evidence)

Adverse events

One study showed no clinically important difference between PCA and spinal epidural for the occurrence of nausea (1 study, n=49, low quality evidence)

One study showed no clinically important difference between PCA and spinal epidural for the occurrence of vomiting (1 study, n=49, low quality evidence)

One study showed no clinically important difference between PCA and spinal epidural for the occurrence respiratory depression (1 study, n=49, low quality evidence)

Evidence not suitable for GRADE analysis

Pain relief

One study showed a statistically significant benefit with spinal epidural for pain scores compared to PCA at twenty four hours postoperatively (1 study, n=50, high risk of bias).

Length of stay

One study showed no statistically significant difference between PCA and spinal epidural for pain scores at forty eight hours postoperatively (1 study, n=50, high risk of bias).

One study found no difference in length of hospital stay between groups (n=50, high risk of bias).

Spinal epidural compared to continuous epidural for pain management

One study showed a clinically important benefit with spinal epidural for clavien dindo grade I complications compared to continuous epidural (1 study, n=80, low quality evidence)

One study showed no clinically important difference between spinal epidural and continuous epidural for clavien dindo grade II complications (1 study, n=80, low quality evidence)

One study showed a clinically important harm with spinal epidural for clavien dindo grade III complications compared to continuous epidural (1 study, n=80, low quality evidence)

One study showed no clinically important difference between spinal epidural and continuous epidural for clavien dindo grade IV complications (1 study, n=80, low quality evidence)

Evidence not suitable for GRADE analysis

Pain relief

One study showed no statistically significant difference between spinal epidural and continuous epidural in pain scores (1 study, n=80, very high risk of bias)

Rescue medication

One study showed a statistically significant benefit with spiral epidural for opioid consumption compared to continuous epidural (1 study, n=80, high risk of bias)

Length of stay

One study reported a statistically significantly benefit with spinal epidural for length of hospital stay compared to continuous epidural, (1 study, n=80, low risk of bias)

One study showed a trend to benefit benefit with spinal epidural for length of ICU stay compared to continuous epidural, (1 study, n=80, low risk of bias)

Quality of life

One study showed no statistically significant difference between spinal epidural and continuous epidural in quality of life (1 study, n=80, high risk of bias)

3.9.2 Health economic evidence statements

- No relevant economic evaluations were identified.

4 Intravenous ketamine

4.1 Review question: What is the clinical and cost effectiveness of adding IV ketamine to IV opioids in managing acute post-operative pain?

4.2 PICO table

For full details see the review protocol in appendices.

Table 50: PICO characteristics of review question

Population	Adults (18 years and older) who have undergone surgery.
Interventions	• IV opioids + IV ketamine
Comparisons	• IV opioids + placebo

Outcomes	CRITICAL:
	• health-related quality of life
	• pain reduction
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• amount of additional medication use
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• adverse events (including respiratory depression, nausea, vomiting)
	IMPORTANT:
	• psychological distress and mental well-being
	• symptom scores
	• functional measures
	• length of stay in intensive care
	• length of stay in hospital
	• hospital readmission

Study design	Randomised controlled trials and systematic reviews of randomised controlled trials.

4.3 Clinical evidence

4.3.1 Included studies

One hundred randomised controlled trials were included in the review;[2, 6, 13-17, 19, 23, 24, 29, 31, 32, 35, 36, 44-46, 48, 50, 59, 60, 62, 66, 72, 73, 77-85, 87, 90, 92, 95, 97, 99, 100, 102, 104, 105, 113, 115, 117-120, 122-126, 129, 131, 137, 138, 142, 143, 145, 147, 157, 159, 161-163, 166, 167, 169, 173, 176, 183, 185, 192-194, 199, 201, 202, 207, 209, 211, 212, 217, 218, 221, 222, 225, 237, 238, 246, 250, 253-255, 257] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See appendices for the study selection flow chart, study evidence tables, forest plots and GRADE tables.

4.3.2 Excluded studies

See the excluded studies list in appendices.

4.3.3 Summary of clinical studies included in the evidence review

Table 51: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Adam 2005[2]	**Ketamine + Opioid:** 0.05 mL/kg IV ketamine given 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 $\mu g \cdot kg^{1} \cdot min^{1}$ of ketamine continued until the patient emerged from anaesthesia. Infusion rate reduced to 1.5 $\mu g \cdot kg^{1} \cdot min^{1}$ and maintained for 48 h. Pain was initially controlled in the PACU by titrating boluses of 3 mg morphine every 5 min until VAS score was <30 mm. 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. n=21 **Opioid:** Identical volume of saline. Pain was initially controlled in the	ASA physical status I–III patients. All were scheduled to undergo elective total knee arthroplasty with general anesthesia. France	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	PACU by titrating boluses of 3 mg morphine every 5 min until VAS score was <30 mm. 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. n=21			
Akhavanakbari 2014[6]	**Ketamine + Opioid:** PCA morphine 0.2 mg/ml + ketamine 1 mg/ml; or morphine 0.1 mg/ml + ketamine 2 mg/ml+ ketamine1 mg/ml n=40 **Opioid:** PCA morphine 0.2 mg/ml n=20	Patients were ASA physical status I–II, aged 20-60 and underwent orthopaedic surgery. Iran	• Pain • Additional medication	
Arikan 2016[13]	**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	ASA physical status I and II patients, aged 30-60 years, scheduled to undergo elective open total abdominal hysterectomy. Turkey	• Pain • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	morphine. n=40 **Opioid:** 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. n=40			
Aubrun 2008[14]	**Ketamine + Opioid:** Post-operatively 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. n=45 **Opioid:** Post-operatively patients were connected to PCA andreceived Morphine 1mg mL-1 lockout period 7 min. n=45	Women aged 18-70 yr, ASA 1-2, weighing between 50 and 100 kg, and undergoing elective abdominal gynaecological surgery. France	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
Aveline 2006[16]	**Ketamine + Opioid:** Preoperatively received morphine 0.1mgkg-1and	ASA 1-2, scheduled for elective surgical lumbar discectomy with partial	• Pain • Additional medication • Adverse events:	

Study	Intervention and comparison	Population	Outcomes	Comments
	ketamine 0.15 mgkg-1. Postoperatively in PACU PCA morphine with 7 min lockout. n=23 **Opioid:** Preoperatively received Morphine 0.1 mgkg-1. In PACU PCA morphine 1mg with 7 min lockout. n=23	laminectomy and nucleotomy. France	○ Nausea and vomiting	
Aveline 2009[15]	**Ketamine + Opioid:** 2 mg.ml ketamine was administered over 20 min. Continuous infusion of 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. n=25 **Opioid:** 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.	ASA physical status I-III undergoing elective unilateral knee replacement under general anaesthesia. France	• Pain • Additional medication • Functional measure • Length of hospital stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	n=24			
Ayoglu 2005[17]	**Ketamine + Opioid:** IV bolus of 0.5mg/kg ketamine slowly and infusion of 0.15 mg/kg for the next 4 hours. 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. n=20 **Opioid:** Saline bolus infusion of the same volume. 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. n=20	ASA I-II patients scheduled for elective laparoscopic cholecystectomy. Turkey	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
Badrinath 2000[19]	**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	ASA physical status I and II female outpatients undergoing breast biopsy procedures under local anaesthesia USA	• Additional medication • Adverse events: ○ Nausea and vomiting • Length of hospital stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	propofol. The study drug solutions consisted of propofol, 9.4 mg/mL, and ketamine, 0, 0.94, 1.88, or 2.83 mg/mL, respectively. n=75 **Opioid:** Propofol/saline (10:1; 5:1 or 3.3:1); a standard volume of 1.2 mL saline was added to 20 mL of propofol. The study drug solutions consisted of propofol, 9.4 mg/mL. n=25			
Bauchat 2011[23]	**Ketamine + Opioid:** Patients received receiving hyperbaric spinal bupivacaine, fentanyl and morphine. Additional 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 scheduled 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	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 USA	• Pain • Additional medication • Adverse events ○ Nausea & Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n= 94 **Opioid:** Patients received receiving hyperbaric spinal bupivacaine, fentanyl and morphine. Additionally 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. n= 94			
Bilgen 2012[29]	**Ketamine + Opioid:**	ASA 1-2 term pregnant, nulliparous women in whom	• Pain	

Study	Intervention and comparison	Population	Outcomes	Comments
	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 n= 105 **Opioid:** 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	cesarean delivery was indicated Turkey	• Additional medication • Adverse events ○ Nausea & Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	n=35			
Burstal 2001[31]	**Ketamine + Opioid:** PCA morphine 1mg/ml and ketamine 2 mg/ml. PCA was commenced on return of cognitive function. n=37 **Opioid:** PCA morphine 1 mg/ml n=33	All patients presenting for total abdominal hysterectomy. Australia	• Pain • Adverse events: ○ Nausea • Psychological distress and mental well-being	
Cagla Ozbakis Akkurt 2009[32]	**Ketamine + Opioid:** - 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. n=20 **Opioid:** 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	ASA1-2 patients scheduled for arthroscopy under spinal anaesthesia were enrolled. Turkey	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	total Meperidine dose did not exceed a maximum of 2 mg/kg in any 4 hours. n=20			

Cengiz 2014[35]	**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 IV morphine, with a lockout period of 5 minutes and no background infusion or limits.
	n=30
	
	Opioid:
	A similar volume of saline 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
		Patients aged 18 - 65 years, ASA grade I, II or III, who were scheduled for total knee arthroplasty surgery under general anaesthesia.
		
		Turkey
			• Pain
			• Additional medication
			• Adverse events:
			  ○ Nausea
			  ○ Vomiting
				As additional analgesia; all patients were ordered 1000 mg paracetamol intravenously, every 8 hours for 24 hours, to be administered.

Study	Intervention and comparison	Population	Outcomes	Comments
	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 IV morphine, with a lockout period of 5 minutes and no background infusion or limits. n=30			
Chazan 2010[36]	**Ketamine + Opioid:** PCA morphine + ketamine (1.0 mg + 5 mg respectively) with 7 min lockout period, in case of insufficient pain control by PCA im Diclofenac 75 mg was available every 6 hours n=24 **Opioid:** PCA 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 n=22	Patients scheduled for elective transthoracic MIDCA, OPCAB or lung surgery under general anaesthesia were recruited. Israel	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
D'Alonzo 2011[44]	**Ketamine + Opioid:** Received 0.5 mg/kg of intravenous ketamine IV prior to chest wall incision. Postoperatively: Ketorolac (dose not specified) & Epidural	Inclusion criteria not specified USA	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	(medications not specified) n=21 **Opioid:** Normal saline equivalent of Ketamine bolus. Postoperatively: Ketorolac (dose not specified) & Epidural (medications not specified) n=20			

Dahi-Taleghani 2014[45]	**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.
	n=70
	
	Opioid:
	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.
	n=70
		All male patients, aged 18-65 years undergoing orthopaedic surgery with history of opium abuse.
		
		Iran
			• Pain
			• Additional medication
			• Adverse events:
			  ○ Nausea
			  ○ Vomiting	

Dahl 2000[46]	**Ketamine + Opioid:**	Adult women, ASA physical	• Pain	Pre-incisional and intraoperative

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=60 **Opioid:** 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. n=29	status I–III, undergoing elective abdominal hysterectomy procedures. USA	• Additional medication	ketamine groups merged for analysis. All patients were given acetaminophen 1 g sup three times daily.

Darwish 2005[48]	**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.
		Adult patients who were scheduled to open colorectal surgery lasting at least 3 hours. All patients were ASA 1-3.
		
		Estonia
			• Pain
			• Additional medication
			• Adverse events:
			  ○ Nausea
			  ○ Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	During the postoperative period 3 mg of morphine was given iv at 5 min intervals until behavioural pain score was<1 In PACU PCA morphine 1 mg as an iv bolus lockout interval 15 min n=30 **Opioid:** 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 behavioural pain score was<1 In PACU PCA morphine 1 mg as an iv bolus lockout interval 15 min n=30			
Deng 2009[50]	**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	Patients who underwent major surgery for lower limb fracture were involved. China	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=150 **Opioid:** 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. n=50			
Duale 2009[59]	**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	Patients aged 20-75 years of age scheduled for elective partial pneumonectomy under thoracotomy France	• Pain • Additional medication • Adverse events ○ Nausea & Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	n=42 **Opioid:** Isotonic saline given in the same volume as Ketamine protocol. n= 44 **Both groups**: 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)			
Edwards 1993[62]	**Ketamine + Opioid:** Morphine 1 $mg.h^{-1}$ plus ketamine (5 $mg.h^{-1}$, 10 $mg.h^{-1}$; and 20 $mg.h^{-1}$). Immediately after surgery, each patient was connected to a PCA infusion pump, which was programmed to deliver a 1 mg bolus of morphine with a lockout time of	Patients aged greater than 60 years old undergoing elective upper abdominal surgery. UK	• Pain • Additional medication • Adverse events: ○ Respiratory depression	

Study	Intervention and comparison	Population	Outcomes	Comments
	5 min. n=30 **Opioid:** Morphine 1 mg.h^{-1}. Immediately after surgery, each patient was connected to PCA infusion pump, which was programmed to deliver a 1 mg bolus of morphine with a lockout time of 5 min. n= 10			
Fiorelli 2015[66]	**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 which offered a maximum of 1 mg of morphine at 7-min intervals. n=38 **Opioid:** Placebo group received an equivalent i.v. volume of normal saline. The postoperative analgesia was performed by	Consecutive patients planned for an elective partial pneumonectomy by standard lateral thoracotomy for management of non-small-cell lung cancer. Italy	• Pain • Additional medication • Adverse events: ○ Nausea & Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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 which offered a maximum of 1 mg of morphine at 7-min intervals. n=37			
Ganne 2005[72]	**Ketamine + Opioid:** IV ketamine just before induction (0.15milligrams /kg-1) followed by a continuous infusion during anesthesia (2 micrograms/kg-1min-1). n=31 **Opioid:** Saline bolus just before induction and continuous infusion of saline during anesthesia n=31 **Both groups**: 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	Inclusion criteria not specified France	• Additional medication • Adverse events: ○ Nausea & Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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.			
Garg 2016[73]	**Ketamine + Opioid:** 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 n=22 **Opioid:** 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 n=22	ASA 1 and 2 patients aged 18 to 60, scheduled to undergo selective spine surgery. India	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
Ghazi-Saidi K 2002[77]	**Ketamine + Opioid:** Pre-emptive low-dose ketamine (0.2 mg/kg) administered prior to anaesthesia. 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. n=27 **Opioid:** Standardized general anaesthesia. 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. n=26	ASA physical status I and II women who were candidates for caesarean section under general anaesthesia. Iran	• Pain • Additional medication	
Gillies 2007[78]	**Ketamine + Opioid:** Ketamine 0.25 mg/kg given as a constant IV infusion over 10 minutes. IV morphine continued to be administered as needed. First dose of morphine 4 mg and then 2 mg increments as	Patients who required more than two doses of morphine in the recovery room, had a pain score ≥5 on a standard VRS, a sedation score ≤1 and a respiratory rate greater than eight.	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	required. Patients received morphine 2 mg as initial bolus for postoperative pain followed by 1 mg increments. n=19 **Opioid:** Normal Saline given as a constant IV infusion over 10 minutes. IV morphine continued to be administered as needed. First dose of morphine 4 mg and then 2 mg increments as required. Patients received morphine 2 mg as initial bolus for postoperative pain followed by 1 mg increments. n=22	Australia		
Guignard 2002[79]	**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. 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·kg1·min-1 in the folg·kg-1·min-1 lowing 24 h.	Adults older than 18 yr were included if they were scheduled to have major abdominal surgery and postoperative management and ventilation in a SICU. France	• Pain • Additional medication • Adverse events: ○ Nausea	

Study	Intervention and comparison	Population	Outcomes	Comments
	n=47 **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. Ketamine was replaced by saline serum and was administered under the same conditions. Ketamine or placebo was administered simultaneously with the titration of morphine. A nurse not involved in the care of the patients prepared the syringes of ketamine or placebo. No additional analgesia or sedation was administered to patients during their SICU stay. n=54			
Guillou 2003[80]	**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.	Adults scheduled to have major abdominal surgery and postoperative management and ventilation in a SICU. France	• Pain • Additional medication • Adverse events: ○ Nausea	

Study	Intervention and comparison	Population	Outcomes	Comments
	Ketamine was administered separately with an initial bolus of 0.5 mg/kg followed by a perfusion of 2 during the first 24h and 1g.kg^{1}·min^{1} in the folg·kg^{1}·min^{1} lowing 24 h. n=47 **Opioid:** 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. Saline serum and was administered under the same conditions, administered simultaneously with the titration of morphine. n=54			
Hadi 2009[81]	**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	Patients who had a physical status class I-II ASA, scheduled for scoliosis surgery. Jordan	• Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	set to deliver morphine solution (1 mg/ml) at the rate of 3–5 mg/hr in the PACU. n=20 **Opioid:** 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. n=20			
Hadi 2010[82]	**Ketamine + Opioid:** Anaesthesia 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 n=15 **Opioid:** Anaesthesia was pre-induced using remifentanil 1µ/kg in both groups followed by remifentanil infusion at a dose of 0.2µg/kg/minute normal saline	Patients scheduled for posterior lumbar and thoracic spinal fusion surgery. Hungary	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	0.9% n=15			
Hadi 2013[83]	**Ketamine (peri-operatively) + Opioid:** 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. Ketamine (1 µg/kg/min) both intra- and postoperatively n=15 **Ketamine (post-operatively) + Opioid:** 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. Ketamine (1 µg/kg/min) postoperatively. n=15 **Opioid:** 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. Saline given in place of ketamine intra and postoperatively. n=15	Adult 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 microdiscectomy surgery. Hungary	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
Haliloglu 2016[84]	**Ketamine + Opioid:** Bolus dose 10 ml ketamine (5mg ml^{-1}). Infusion during maintenance 50 ml of ketamine (2 mg ml-1). Ketamine bolus of 0.5 mg kg-1 IV administered at the time of induction of general anaesthesia. After induction, a ketamine infusion of 10µg kg-1 min-1 was started and discontinued at the end of the surgery. Started and discontinued at the end of the surgery was started and discontinued at the end of the surgery. n=26 **Opioid:** Bolus dose 10 ml of normal saline. For infusion normal saline was used. n=26	ASA I-II scheduled for elective caesarean section. Turkey	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
Han 2013[85]	**Ketamine + Opioid:** 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	Pregnant mothers of ASA class 1-2, between 37-42 weeks of pregnancy, who were scheduled for caesarean section under spinal anaesthesia. South Korea	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	dose. n=20 **Opioid:** 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. n=20			
Hasanein 2011[87]	**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. n=30 **Opioid:** For maintenance of anesthesia, continuous infusion of propofol 6–10 mg/kg/h was started; the	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. Egypt	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=30			
Hayes 2004[90]	**Ketamine + Opioid:** Received a pre-induction 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). n=22 **Opioid:** 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) n=23	Patients who had lower limb amputation because of peripheral vascular disease, cancer or chronic infection Australia	• Pain • Additional medication	
Hong 2011[92]	**Ketamine + Opioid:** The ketamine group was injected with 0.3 mg/kg of ketamine during induction and	patients classified as ASA 1 or 2 scheduled for laparoscopic gynecologic surgery under general anesthesia were the objects	• Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	continuously infused with 3 µg/kg/min of ketamine during surgery. n= 20 **Opioid:** The control group was injected and infused with normal saline at the same volumes as the ketamine group. n=20 **Both groups:** 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.	of study. South Korea		

Study	Intervention and comparison	Population	Outcomes	Comments
Ilkjaer 1998[95]	**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. n=30 **Opioid:** 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	Patients undergoing elective nephrectomy or operation on pelvic structures. Denmark	• Pain • Additional medication	Control group received bolus dose of Ketmamine after induction.

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=30			
Jaksch 2002[97]	**Ketamine + Opioid:** Received an IV bolus of 5 mg/mL Ketamine after the induction of anaesthesia. Thereafter a continuous infusion of the drug was started using a second syringe, with a capacity of 50 mL, contained 2 mg/mL of 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 a bolus every 8 min maximally with no background infusion and no hourly limit. n=15 **Opioid:**	Patients aged 19yrs or older and ASA physical status I or II. Enrolled patients scheduled for elective arthroscopic anterior cruciate ligament repair with or without meniscus repair. Austria	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	Received an isotonic sodium chloride solution in both the bolus and the infusion. 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 a bolus every 8 min maximally with no background infusion and no hourly limit. n=15			
Javery 1996[99]	**Ketamine + Opioid:** IV PCA consisting of morphine with ketamine 1 mg. m1-1 of each. PCA pumps programmed to deliver 1 ml of solution with a lockout of six minutes. n=22 **Opioid:** IVPCA consisting of morphine 1 mg. PCA pumps programmed to deliver 1 ml of solution with a lockout of six minutes. n=20	ASA 1 and 2 patients between the ages of 21 and 55yrs due to undergo elective lumbar microdiscectomy. USA	• Pain • Additional medication • Adverse events: ○ Nausea	
Jendoubi 2017[100]	**Ketamine + Opioid:**	Patients aged ≥18 years and	• Pain	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=20 **Opioid:** Received an equal volume of normal saline 0.9%. In the PACU, pain was controlled by titration of IV morphine. n=20	the American Society of Anesthesiologists (ASA) physical Class I or II undergoing elective open nephrectomy. Tunisia	• Additional medication • Adverse events: ○ Nausea and vomiting • Phsychological distress • Length of hospital stay • Functional capacity	
Joly 2005[102]	**Ketamine + Opioid:** Remifentanil ketamine: intraoperative infusion of remifentanil at a rate 0.4g kg^{-1} min^{-1} and ketamine. Within 4h 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. n=24 **Opioid:** Remifentanil (0.05 µg kg-1 min-	Adult patients who were scheduled to undergo open colorectal surgery lasting at least 2 h. ASA physical status I–III. France	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	1, or 0.4 µg kg-1 min-1) and saline placebo infusion. 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. n=50			
Kapfer 2005[104]	**Ketamine + Opioid:** Ketamine 10 mg over 12 min. Morphine titration (3 mg every 5 min) was resumed until the VRS was <2 or until 60 min had elapsed. Opioid given after the test drugs was considered supplemental morphine. n=22 **Opioid:** Isotonic saline over 12 min. Morphine titration (3 mg every 5 min) was resumed until the VRS was <2 or until 60 min had elapsed. Opioid given after the test drugs was considered supplemental morphine. n=21	Patients 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 anaesthesia. USA	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
Katz 2004[105]	**Ketamine (pre-op) + 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.	Patients scheduled for radical prostatectomy for prostate cancer.	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	Continuous intraoperative i.v. fentanyl. n=47 **Ketamine (post-op) + 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. Continuous intraoperative i.v. fentanyl. n=50 **Opioid:** Pre-incision saline and post-incision saline. Continuous intraoperative i.v. fentanyl. n=46	Canada		

Kim 2013[113]	**Ketamine + Opioid:**
	Ketamine infusion of 1µg/kg/min following bolus 0.5 mg/kg or infusion of 2µg/kg/min following bolus 0.5mg/kg of ketamine, started before skin incision intraoperatively, and continued for 4 hours. Post-operatively patients were administered fentanyl using IV-PCA (bolus dose 15µg of fentanyl, lockout interval of 5min, no basal infusion).
	n=35
		Healthy patients with an ASA of I-II, aged between 28 and 70 years old, and who were scheduled for elective major lumbar spinal surgery. The type of surgery was posterior decompression and posterior lumbar interbody fusion with instrumentation.
		
		South Korea
			• Pain
			• Additional medication
			• Adverse events:
			  ○ Nausea
			  ○ Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	Opioid: 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). n=17			
Kollender 2008[115]	**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. n=30 **Opioid:** 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. n=30	ASA 1-3 patients scheduled for one or two major bone and soft tissue tumour surgeries. Israel	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting • Psychological distress and mental well-being	
Kotsovolis 2015[117]	**Ketamine + Opioid:** Ketamine group patients were administered 0.3mg/kg	ASA 1 and 2 patients aged 18-79 years undergoing Laparoscopic	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=28 **Opioid:** Placebo group received only placebo. In cases of supplementary analgesia 1000 mg paracetamol was administered. n=28	Cholecystectomy. Greece	• Adverse events: ○ Nausea and vomiting	
Kwok 2004[118]	**Ketamine (pre-op) + Opioid:** IV ketamine 0.15 mg/kg (made up to 10 mL with normal saline) immediately before the induction of anaesthesia 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 analogue scale (VAS) pain score was <20 mm. On the ward, patients received	Women, ASA physical status I or II, aged between 18 and 65 yr, scheduled for laparoscopic gynaecologic surgery. Hong Kong	• Pain • Additional medication • Length of hospital stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	IM morphine 0.15 mg/kg every 4h. n=45 **Ketamine (post-op) + Opioid:** Saline before the induction of anaesthesia 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 analogue scale (VAS) pain score was <20 mm. On the ward, patients received IM morphine 0.15 mg/kg every 4h. n=45 **Opioid:** Normal saline before the induction of anaesthesia 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 analogue scale (VAS) pain score was <20 mm. On the ward, patients received IM morphine 0.15 mg/kg every 4h. n=45			

Study	Intervention and comparison	Population	Outcomes	Comments
Lahtinen 2004[119]	**Ketamine + Opioid:** Received a 75 ug/kg bolus of ketamine in 15 mL of normal saline. Bolus dosing (15 min) of either ketamine was followed by continuous infusion of ketamine 1.25 ug·kg^{-1}·min^{-1} for 48 h after arrival to the 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 developed. After opioid titration and repeating the instructions, the patients had access to oxycodone with a PCA device: bolus dose, 2 mg; dose duration, 2 min; lockout interval, 13 min (15-min effective lockout time). n=48 **Opioid:** Received a 15-mL bolus of normal saline from a syringe with an identical appearance followed by continuous infusion of placebo infusion at the same rate for 48 h after arrival. A PACU nurse administered oxycodone as 2-mg boluses every 10 min until the VAS score at rest was <3 or until excessive sedation developed.	Patients scheduled for elective coronary artery bypass grafting with cardiopulmonary bypass and younger than 70 yr of age were considered eligible for the study. Finland	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting • Psychological distress and mental well-being	

Study	Intervention and comparison	Population	Outcomes	Comments
	After opioid titration and repeating the instructions, the patients had access to oxycodone with a PCA device: bolus dose, 2 mg; dose duration, 2 min; lockout interval, 13 min (15-min effective lockout time). n=51			
Lak 2010[120]	**Ketamine + Opioid:** 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. n=25 **Opioid:** 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	Donors of renal transplantation with ASA I. Iran	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	nurses without any limitations as the loading dose followed by 1 mg every 5 minutes until the VAS became less than 4. n=25			
Launo 2004[122]	**Ketamine + Opioid:** intra operative administration of ketamine (0.7 mg/kg) n=20 **Opioid:** intra operative administration of Tramadol (15 mg/kg) n=20 **Both groups:** All patients received the same anesthesia, which consisted of: 1) premedication: i .v. midazolam (1-2 mg) in or der to control emotional state. 2) Induction: remifentanyl (0 .2-0 .5 µg/kg/min) , propofol (1.5 mg/kg), rocuronium (0 .6 mg/kg) i n 60 s, mask ventilation (air +O2) for 2 min and then tracheal intubation (TI) at the 3rd minute	Patients: a)age >18 years; b) non obese patient (obese patient =patient weight >30% of ideal weight; Lorentz table); c) ASA class I, II , III ; d) elective surgery; e) absence of allergies or intolerance to anesthetics; f) absence of allergies or intolerance to ketamine and tramadol; g) comprehending of Visual Analog Scale (VAS) and Verbal Rating Scale (VRS); h) absence of psychiatric illness (pastor present). Italy	• Pain • Adverse events: ○ Nausea and respiratory depression	
Leal 2013[123]	**Ketamine + Opioid:** Remifentanil (0.4 mcg.kg-1.min-1) and ketamine (5 mcg.kg-1.min-1). Remifentanil was increased or decreased as	Patients aged over 18 years of age, both sexes, ASA I or II, undergoing video laparoscopic cholecystectomy.	• Pain • Additional medication • Adverse events: ○ Nausea and Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n= 20 **Opioid:** 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	Brazil		

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n= 20			
Leal 2015[124]	**Ketamine + Opioid:** 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. n=30	Patients aged ≥18 years, any sex, classified as American Society of ASA I or II, and undergoing laparoscopic cholecystectomy at Hospital SãoPaulo/Federal University of São Paulo Brazil	• Pain • Additional medication • Adverse events: ○ Nausea and Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	Opioid: 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. n=30			
Lee 2014[125]	**Ketamine + Opioid:** Anaesthesia 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 anaesthesia induction, and 3 µg/kg/min was continuously infused during surgery. n=20	Patients aged 20-70 years and of American Society of Anaesthesiologists physical status 1 or 2 scheduled for laparoscopic cholecystectomy under general anaesthesia. South Korea	• Pain	Intraoperative Ketamine

Study	Intervention and comparison	Population	Outcomes	Comments
	Opioid: Anaesthesia 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 anaesthesia induction, and was continuously infused during surgery. n=20			
Lenzmeier 2008[126]	**Ketamine + Opioid:** 0.5mg/kg dose of ketamine by IV bolus with induction of general anesthesia. n=11 **Opioid:** 0.5mg/kg dose of placebo by IV bolus with induction of general anesthesia. n=11 **Both groups:** Opioids given as rescue medication but not specified which opioid or regimen.	Inclusion criteria not specified USA	• Pain • Additional medication	
Li 2016[129]	**Ketamine + Opioid:** Post-operative pain was controlled by titration of IV	Patients scheduled to undergo abdominal surgery, who were between the ages	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	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 infused intravenously with 3 mg/kg/h ketamine. n=17 **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. Infused intravenously with isotonic saline. n=15	of 18 to 70 years, and ASA, grade 1 or 2. China	• Adverse events: ○ Nausea and vomiting	
Lo 2008[131]	**Ketamine + Opioid:** PCA was started in the PACU. The PCA device was programmed to deliver 1-mL doses of medication ketamine and morphine combined with a	Inpatient indicated for hysterectomy with preference for patient-controlled analgesia; No documented allergy to morphine or ketamine.	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	bolus dose of 2 mL permitted and a lock-out time of 6 min. The aim of the lock-out period is to prevent overdose through excessive demands for analgesia. n=15 **Opioid:** PCA was started in the PACU. The PCA device was programmed to deliver 1-mL doses of medication, morphine alone—with a bolus dose of 2 mL permitted and a lock-out time of 6 min. The aim of the lock-out period is to prevent overdose through excessive demands for analgesia. n=15	USA		
Mathisen 1999[137]	**Ketamine (pre-op) + 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. n=20 **Ketamine (post-op) + Opioid:** (R) Ketamine 1.0mg/kg post-operatively. Post-operatively, patients administered PCA meperidine by bolus of 0.1mg/kg with lockout of 5	ASA grade 1-2 patients undergoing elective laparoscopic cholecystectomy. Norway	• Pain • Additional medication	Preoperative ketamine & Postoperative ketamine combined

Study	Intervention and comparison	Population	Outcomes	Comments
	minutes continued for 4 hours. n=20 **Opioid:** 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. n=20			
McKay 2007[138]	**Ketamine + Opioid:** 2.5ug/kg/min ketamine plus PCA morphine 1mg with 6 minute lockout. n=19 **Opioid:** Saline plus PCA morphine 1mg with 6 minute lockout. n=22	Patients having bowel resection. Canada	• Pain • Additional medication • Adverse events: ○ Nausea • Length of stay in hospital	Postoperative ketamine
Menigaux 2000[142]	**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	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 France	• Pain • Additional medication • Functional measure ○ Knee flexion	

Study	Intervention and comparison	Population	Outcomes	Comments
	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 n=30 **Opioid:** In the control 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,			

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n= 15			
Menigaux 2001[143]	**Ketamine + Opioid:** After anesthetic induction, 0.15 mg/kg ketamine diluted in isotonic sodium chloride solution was injected IV n=25 **Opioid:** After anesthetic induction, a 10-mL syringe containing either isotonic sodium chloride was injected IV n=25 **Both groups:** 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	Patients aged 18 - 60 scheduled to undergo elective arthroscopic meniscal surgery France	• Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	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.			
Michelet 2007[145]	**Ketamine + Opioid:** PCA device, 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.	Aged of 18 yr or older, planned lobectomy by posterolateral thoracotomy incision, and the choice of PCA in preference to other forms of postoperative analgesia. France	• Pain score • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	n= 25 **Opioid:** PCA device, 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. n=25			
Miziara 2016[147]	**Ketamine + Opioid:** before surgery, continuous S(+)-ketamine infusion at a rate of 0.3mg·kg−1 ·h−1. Morphine was administered at a dose of	Patients aged 18–65 years with American Society of ASA 1-2.	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=24 **Opioid:** 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. n= 24	Brazil		
Moro 2017[157]	**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,	135 patients aged 18-65 years old, With an ASA Physical status I or II, who where scheduled to undergo laparoscopic cholecystectomy Brazil	• Pain • Additional medication • Nausea and vomiting • Lengh of stay in PACU	

Study	Intervention and comparison	Population	Outcomes	Comments
	tramadol (100mg) was administered IV at eight-hour minimum intervals. n=90 **Opioid:** 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. n=45			
Morue 2018[159]	**Ketamine + Opioid:** Received conscious sedation with the ketamine infusion and a TCI of remifentanil titrated to	Female patients undergoing oocyte retrieval by transvaginal ultrasound-guided ovarian puncture.	• Pain • Additional medication • Adverse events: ○ Nausea, vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	maintain a pain VAS equal to or less than 30 mmm. Ketamine 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 pump was used for the remifentanil infusion. 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. Concentration was increased in increments of 1ngml-1 until the pain experienced by the patient was less than 30 mm on VAS. n=67 **Opioid:** Received 0.9% saline infusion and a TCI of remifentanil titrated to maintain a pain VAS equal to or less than 30 mmm. A TCI pump was used for the remifentanil infusion. A concentration of 2 ng ml-1 of remifentanil was established before the start of the	Belgium	and respiratory depression • Length of stay in PACU	

Study	Intervention and comparison	Population	Outcomes	Comments
	procedure, and the surgeon waited until 2 min before the first painful stimulation. Concentration was increased in increments of 1ngml-1 until the pain experienced by the patient was less than 30 mm on VAS. n=65			
Murdoch 2002[161]	**Ketamine + Opioid:** During the procedure, morphine was administered from the patients PCA syringe. Patients 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 n=21 **Opioid:** During the procedure, morphine was administered from the patients PCA syringe. 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.	ASA grade 1-2 patients entered the study and underwent elective total abdominal hysterectomy with or without bilateral salping-oopherectomy. UK	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	n=21			
Nesher 2008[163]	**Ketamine + Opioid:** PCA drug bolus injections consisted of 1mg morphine + 5 mg ketamine. The device was pre-set to deliver bolus whenever patient activated it, controlled by 7 min lockout period. If pain was not attenuated within 30 min of initial activation, a rescue dose of im diclofenac was available. n=30 **Opioid:** PCA drug bolus injections consisted of 1.5 mg morphine alone. The device was pre-set to deliver bolus whenever patient activated it, controlled by 7 min lockout period. if pain was not attenuated within 30 min of initial activation, a rescue dose of im diclofenac was available. n=30	Patients scheduled for elective Minimally Invasive Direct Coronary Artery Bypass or Off-pump coronary artery bypass or for lung resection via anterolateral thoracotomy were enrolled. Israel	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
Nesher 2009[162]	**Ketamine + Opioid:** Drug injections consisted of 1mg morphine plus 5 mg ketamine bolus. A blinded anesthesiologist administered the first dose, after which the PCIA device was turned on.	Patients referred for a first time isolated coronary bypass and if their surgeon considered them candidates for a Minimally Invasive Direct Coronary Artery Bypass procedure, or if they	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	The device was pre-set to deliver similar boluses whenever the patient activated it, controlled by a 7-min lockout period. n=22 **Opioid:** Drug injections consisted of 1.5mg morphine plus saline infusion. A blinded anesthesiologist administered the first dose, after which the PCIA device was turned on. The device was pre-set to deliver similar boluses whenever the patient activated it, controlled by a 7-min lockout period. n=22	were to undergo lung surgery. Israel		
Nielsen 2017[166]	**Ketamine + Opioid:** 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	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	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=75 **Opioid:** 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	kg/m² Denmark		

Study	Intervention and comparison	Population	Outcomes	Comments
	administered by nurse in PACU for the first postoperative hour in case the PCA was insufficient. n= 75 **Both groups:** 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.			
Nistal-Nuno 2014[168]	**Ketamine + Opioid:** Received 0.5 mg/kg intravenous ketamine before surgical incision. Morphine administered through PCA as a basal infusion and the incremental supplemental bolus required by the patient. n=24 **Opioid:** Received saline before surgical incision. Morphine administered through PCA as a basal infusion and the incremental supplemental bolus required by	Patients aged between 18 and 75 years, normal Body Mass Index (18.5–24.9), ASA class I, II or III, undergoing elective surgery with surgery time between 60–150 min. USA	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	the patient. n=24			
Nourozi 2010[169]	**Ketamine + Opioid:** IV administration of drugs was done in the post anaesthesia care unit immediately after awakening the patient when he/she was conscious. Prescribed regimen was 5 mg pethidine and 0.25mg kg-1 ketamine. n=25 **Opioid:** IV administration of drugs was done in the post anaesthesia care unit immediately after awakening the patient when he/she was conscious. Prescribed regimen was pethidine 10 mg. n=25	Patients aged 15-60 years who were candidates for elective major abdominal operations were enrolled into the study. Iran	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
Ong 2001[173]	**Ketamine + Opioid:** Patients received a ketamine bolus of 0.3 mg/kg diluted in 10 mg/ml dilution prior to induction. n=20 **Opioid:** Patients received a corresponding volume of	ASA I and II patients aged 17–50 Australia	• Pain • Additional medication • Length of stay • Adverse events: ○ Vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	normal saline prior to induction. n= 20 **Both groups**: Rescue medication was given in the form of i.v. fentanyl boluses of 25 µg, oral Panadeine Forte 1 g and Oxycodone 10 mg.			
Pacreu 2012[176]	**Ketamine + Opioid:** Pre-incisional bolus of IV racemic Ketamine 0.5mg/kg, followed by an infusion of 2.5 micrograms/kg/minute. Postoperatively, 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. n=11 **Opioid:** Pre-incisional bolus of saline, followed by a saline infusion. Postoperatively, 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. n=11	ASA I - III scheduled for multi-level lumbar arthrodesis Spain	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
Parikh 2011[183]	**Ketamine + Opioid:** Bolus dose, 10 ml ketamine (1 mg/ml. Infusion during maintenance, 50 ml of ketamine (1 mg/ml). n=30 **Opioid:** Bolus dose, 10 ml of normal saline was used in group C For infusion during maintenance, 50 ml of normal saline. n=30	Adult patients ASA I and II, 18-70 years of age, scheduled for open renal surgery under general anaesthesia. India	• Pain • Additional medication • Adverse events: ○ Nausea, vomiting and respiratory depression	
Perrin 2009[185]	**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. n=5 **Opioid:** 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.	Patients for elective unilateral, two or three total knee arthroplasty with an ASA I – III Australia	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	n=7 **Both groups:** 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.			
Reeves 2001[192]	**Ketamine + Opioid:** PCA consisting morphine 1 mg/mL plus ketamine 1mg/mL n=36 **Opioid:** PCA morphine 1 mg/mL n=36	All patients presenting for elective major abdominal surgery involving a midline incision were identified. Australia	• Additional medication	The settings for the PCA (bolus size, lock-out interval, and background infusion) were determined by the anaesthesiologist.
Remerand 2009[193]	**Ketamine + Opioid:** Between induction and skin incision, patients received an IV	All adult patients scheduled for a nononcologic Total Hip Arthroplasty	• Pain • Additional medication • Length of stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	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) n=80 **Opioid:** Patients received a similar blinded saline bolus and infusion (equivalent to Ketamine infusion) n=80	France	• Functional measures ○ First transfer, first steps	
Reza 2010[194]	**Ketamine + Opioid:** Received 0.5 mg/kg intravenous ketamine (diluted to 10 mL with normal saline). After the delivery of fetus, 10 IU oxytocin, 2µg/kg fentanyl and 0.15 mg/kg of morphine were used IV. n=30 **Opioid:** Received 10 mL with normal saline. After the delivery of fetus, 10 IU oxytocin, 2µg/kg fentanyl and 0.15 mg/kg of morphine were used IV. n=30	women with ASA status 1 and 2, who requested general anaesthesia for their elective caesarean section Iran	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
Roytblat 1993[199]	**Ketamine + Opioid:** Ketamine IV, 0.15 mg/kg 5 min before surgical incision. Both groups were treated with PCA in exactly the same way, by boluses of 2 mg of morphine with a lockout period of 10 min. A background infusion of morphine of 1 mg/h was provided. This regimen of PCA was continued in the surgical department for 24 h, during which no other analgesics were administered. n=11 **Opioid:** Saline given as control. Both groups were treated with PCA in exactly the same way, by boluses of 2 mg of morphine with a lockout period of 10 min. Abackground infusion of morphine of 1 mg/h was provided. This regimen of PCA was continued in the surgical department for 24 h, during which no other analgesics were administered. n=11	Women, ASA grade I and 11, undergoing elective open cholecystectomy via a subcostal incision. Israel	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
Safavi 2011[201]	**Ketamine + Opioid:** IV ketamine 1 mg/kg plus subcutaneous infiltration of saline, before surgery.	ASA physical status I-II patients, aged 18–60 years old, scheduled for open cholecystectomy.	• Pain • Additional medication • Length of ICU stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	Morphine 0.1 mg/kg was administered for intraoperative analgesia intravenously. n=30 **Opioid:** Subcutaneous infiltration of normal saline 20 mL plus IV saline before surgery. Morphine 0.1 mg/kg was administered for intraoperative analgesia intravenously. n=30	Iran	• Adverse events: ○ Nausea and vomiting	
Sahin 2004[202]	**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. n=17 **Opioid:** 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. n=14	ASA 1nd 2 patients scheduled for lumbar discectomy. Turkey	• Pain • Additional medication	
Singh 2013[207]	**Ketamine + Opioid:** Patients received ketamine in	Adult patients with ASA grades 1 and 2 and	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	dose 1mg/kg or 0.75 mg/kg or 0.5 mg/kg. Patients were informed before the surgery that they can request an analgesic if they feel pain which was administered using iv fentanyl 1g/kg. furthermore supplemental analgesia was administered using iv boluses of fentanyl 1g/kg as an when patient requested n=60 **Opioid:** Isotonic saline. Patients were informed before the surgery that they can request an analgesic if they feel pain which was administered using iv fentanyl 1g/kg. Furthermore supplemental analgesia was administered using iv boluses of fentanyl 1g/kg as an when patient requested. n=20	scheduled for laparoscopic cholecystectomy using a standardized general anaesthesia technique. India	• Adverse events: ○ Nausea and vomiting	
Snijdelaar 2004[209]	**Ketamine + Opioid:** The PCA system was programmed to deliver a bolus of 0.5 ml, corresponding to a bolus dose of 0.5 mg ketamine plus 1 mg of morphine. n=14 **Opioid:**	Men scheduled for radical retropubic prostatectomy, ASA class 1-3. Canada	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	The PCA system was programmed to deliver a bolus of 0.5 ml with saline, corresponding to 1 mg morphine. n=14			
Song 2013[211]	**Ketamine + Opioid:** Immediately after the induction of anaesthesia, 0.3mgkg-1 of ketamine was injected 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. n=25 **Opioid:** 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	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. South Korea	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting •	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=25			
Stubhaug 1997[217]	**Ketamine + Opioid:** After induction of anaesthesia but 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. n=10 **Opioid:** Identical volumes of saline. PCA morphine bolus of 1 mg with a 5 min lockout period. Additional morphine was given and recorded by intensive care nurses. n=10	Patients previously healthy (ASA 1 and 2), scheduled for nephrectomy as part of living-donor kidney transplant programme. Norway	• Pain • Additional medication • Adverse events: ○ Nausea	

Study	Intervention and comparison	Population	Outcomes	Comments

Subramaniam 2011[218]	**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.
	n=15
	
	Opioid:
	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.
	n=15
		ASA physical status 1, 2, and 3, who underwent lumbar or thoracolumbar laminectomy and fusion for back pain.
		
		USA
			• Pain
			• Additional medication
			• Adverse events:
			  ○ Nausea
			  ○ Vomiting
			• Length of hospital stay
			• Length of ICU stay
			• Functional measure	

Suzuki 1999[221]	**Ketamine + Opioid:** Morphine 50µg/kg plus Ketamine 50 mg/kgIV 75 mg/kg IV or 100mg/kg IV 15 min before the end of the operation. n=105 **Opioid:** Morphine 50µg/kg with placebo before the end of the surgery.	Patients, ASA I or II, scheduled for elective outpatient surgery. USA	• Pain • Additional medication • Adverse events: ○ Nausea	

Study	Intervention and comparison	Population	Outcomes	Comments
	n=35			

Sveticic 2008[222]	**Ketamine + Opioid:**
	Postoperatively, patients received a bolus of morphine plus ketamine 1.5 mg each
	n=176
	
	Opioid:
	Postoperatively, patients received a bolus of morphine 1.5 mg
	n=176
		Patients undergoing major elective orthopedic surgery were studied.
		
		Switzerland
			• Pain
			• Additional medication
			• Adverse events:
			  ○ Nausea
			  ○ Vomiting
			  ○ Respiratory depression
			•	

Tang 2010[225]	**Ketamine + Opioid:** Sedation was initiated with fentanyl 1μg/kg, administered intravenously over 10 seconds. After 150 seconds, 10 mg/mL Ketamine administered. Immediately propofol, 2 mg mL was administered in all patients at 4 mg/s n=40 **Opioid:** Sedation was initiated with fentanyl 1μg/kg, administered intravenously over 10 seconds. After 150 seconds, 0.05mL/kg of 9 % normal saline administered. Immediately propofol, 2 mg mL was administered in all patients at 4	Women ASA 1 and 2 undergoing outpatient laparoscopic procedures in west china second hospital were included in the study. China	• Pain • Additional medication • Adverse events: ○ Nausea • Length of stay in ICU	

Study	Intervention and comparison	Population	Outcomes	Comments
	mg/s n=40			
Unlugenc 2002[237]	**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. n=22 **Opioid:** 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. n=21	ASA Physical status 1 or 2 patients, between the ages of 18 and 59 years, scheduled for elective major abdominal surgery with general. Turkey	• Pain • Additional medication • Adverse events: ○ Nausea	
Unlugenc 2003[238]	**Ketamine + Opioid:** PCA morphine 0.4mg.mL^{-1} + ketamine 1mg.mL-1. First standardised 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 mg.kg^{-1} every 20min without time limit) with the PCA device. n=30	ASA I-II patients, aged 16-60 yr, scheduled for elective major abdominal surgery with general anaesthesia. Turkey	• Pain • Additional medication • Adverse events: ○ Nausea	

Study	Intervention and comparison	Population	Outcomes	Comments
	Opioid: PCA morphine 0.4mg.mL^{-1}. First standardised 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 mg.kg^{-1} every 20min without time limit) with the PCA device. n=30			
Webb 2007[245]	**Ketamine + Opioid:** Ketamine group: IV ketamine initial dose of 0.3 mg/kg at anaesthetic induction and a ketamine infusion at 0.1 mg kg-1 h-1 for 48 h. In the post anaesthesia 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 post anaesthesia care unit to manage pain uncontrolled by study medications and continued throughout the 48-h study period. Thus, patients had three separate mechanical infusion devices during the study. n=56	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. Australia	• Pain • Adverse events ○ Nausea	

Study	Intervention and comparison	Population	Outcomes	Comments
	Opioid: Control group: An equivalent volume of normal saline at induction followed by a normal saline infusion at equivalent rate to maintain blinding. In the post anaesthesia care unit, patients were given IV morphine boluses 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 post anaesthesia care unit to manage pain uncontrolled by study medications and continued throughout the 48-h study period. Thus, patients had three separate mechanical infusion devices during the study. n=64			
Weinbroum 2003[246]	**Ketamine + Opioid:** 15µg/kg of morphine plus 250 µg/kg of ketamine. n=131 **Opioid:** 30µg/kg of morphine plus saline. Patients were given up to three such IV boluses either	Patients with ASA physical status I to III, scheduled for elective surgery (abdominal general surgery, orthopedic surgery, transthoracic lung biopsy or wedge resection) under general anaesthesia. Israel	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	Higher morphine dose in opioid only group.

Study	Intervention and comparison	Population	Outcomes	Comments
	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 n=114			
Wilder-Smith 1998[250]	**Ketamine + Opioid:** Three minutes before anesthesia induction, patients received fentanyl, intravenous injection. 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. Morphine PCA was started 30 min post extubation 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). PCA morphine was discontinued 24 h postoperatively, and analgesia on the ward continued with per OS diclofenac n=15 **Opioid:**	ASA physical status I or II patients undergoing elective abdominal hysterectomy. Denmark	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	Three minutes before anesthesia induction, patients received fentanyl, intravenous injection. Five minutes before skin incision, 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. Morphine PCA was started 30 min post extubation 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). PCA morphine was discontinued 24 h postoperatively, and analgesia on the ward continued with per OS diclofenac. n=15			
Yalcin 2012[253]	**Ketamine + Opioid:** Received intravenous bolus ketamine 0.5 mg/kg, before the induction of anesthesia. Also received a maintenance infusion of5 µg/kg/min ketamine intraoperatively until skin closure. When VAS score was <5, patients were connected to a PCA device set to deliver 1mg morphine as an iv bolus with a 6-min lockout interva. This PCA regimen was	Patients of ASA physical status I-II scheduled for elective total abdominal hysterectomy. Turkey	• Pain • Additional medication	

Study	Intervention and comparison	Population	Outcomes	Comments
	continued for 48 hrs n=30 **Opioid:** Received physiologic saline before the induction of anaesthesia. When VAS score was <5, patients were connected to a PCA device set to deliver 1 mg morphine as an iv bolus with a 6-min lockout interval; continuous infusion was not allowed. This PCA regimen was continued for 48 hrs n=30			
Yeom 2012[255]	**Ketamine + Opioid:** Intravenous PCA consisting of fentanyl 0.4 μg/ml/kg with ketamine 30 μg/ml/kg n=20 **Opioid:** PCA consisting either of fentanyl 0.4 μg/ml/kg n=20	Patients between the ages of 38-78 years undergoing 1-2 level posterior lumbarspinal fusion. All of the patients were ASA physical status classification 1, 2, or 3. South Korea	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	
Zakine 2008[257]	**Ketamine (pre-op) + Opioid:** PERI group receiving IV bolus of 0.5 mg/kg of ketamine 10min before the incision followed by IV infusion of 2 μg.kg-1.min-1 of ketamine starting after this	Patients over the age of 18 yr scheduled to undergo major abdominal, urologic, or vascular surgery. France	• Pain • Additional medication • Adverse events: ○ Nausea and vomiting	

Study	Intervention and comparison	Population	Outcomes	Comments
	bolus and continued for 48 h postoperatively. In the post-anaesthesia care unit, 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. n=27 **Ketamine (peri-op) + 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 post-anaesthesia care unit, 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			

Study	Intervention and comparison	Population	Outcomes	Comments
	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. n=27 **Opioid:** Control group received placebo. In the post-anaesthesia 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. n=27			

See appendices for full evidence tables.

4.3.4 Quality assessment of clinical studies included in the evidence review

Table 52: Clinical evidence summary: Opioid + Ketamine compared to opioid for post-operative pain

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
Pain: VAS Scale from: 0 to 10.	1505 (25 studies) <6 hours	⨁⨁⨀⨀ VERY LOW1,3 due to inconsistency, imprecision		The mean pain: vas in the control groups was 4.08	The mean pain: vas in the intervention groups was 1.06 lower (1.72 to 0.41 lower)
Pain: VAS Scale from: 0 to 10.	2355 (31 studies) 6-24 hours	⨁⨁⨀⨀ VERY LOW1,3 due to inconsistency, imprecision		The mean pain: vas in the control groups was 2.94	The mean pain: vas in the intervention groups was 0.68 lower (0.96 to 0.41 lower)
Pain-none	33 (1 study) 4 hours	⨁⨀⨀⨀ VERY LOW2,3 due to risk of bias, imprecision	RD 0 (-0.15 to 0.15)	Moderate	
				0 per 1000	0 fewer per 1000 (from 150 fewer to 150 more)
Pain- Mild	33 (1 study) 4 hours	⨁⨁⨁⨀ MODERATE2 due to risk of bias	Peto OR 9.03 (1.93 to 42.26)	Moderate	
				0 per 1000	Not estimable
Pain- Moderate	33 (1 study) 4 hours	⨁⨀⨀⨀ VERY LOW2,3 due to risk of bias, imprecision	RR 0.75 (0.35 to 1.59)	Moderate	
				556 per 1000	139 fewer per 1000 (from 361 fewer to 328 more)
Pain- Severe	33 (1 study) 4 hours	⨁⨀⨀⨀ VERY LOW2,3 due to risk of bias, imprecision	RR 0.56 (0.21 to 1.54)	Moderate	
				444 per 1000	195 fewer per 1000 (from 351 fewer to 240 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
Pain- Very severe	33 (1 study) 4 hours	⨁⊖⊖⊖ VERY LOW2,3 due to risk of bias, imprecision	RR 0.38 (0.03 to 5.38)	Moderate	
				111 per 1000	69 fewer per 1000 (from 108 fewer to 486 more)
Pain-none	63 (2 studies) 24 hours	⨁⊖⊖⊖ VERY LOW2,3 due to risk of bias, imprecision	RR 2.06 (0.56 to 7.55)	Moderate	
				111 per 1000	118 more per 1000 (from 49 fewer to 727 more)
Pain-Mild	63 (2 studies) 24 hours	⨁⨁⊖⊖ LOW3 due to imprecision	RR 0.93 (0.52 to 1.65)	Moderate	
				467 per 1000	33 fewer per 1000 (from 224 fewer to 304 more)
Pain-Moderate	63 (2 studies) 24 hours	⨁⊖⊖⊖ VERY LOW1,3 due to inconsistency, imprecision	RR 0.63 (0.16 to 2.51)	Moderate	
				422 per 1000	156 fewer per 1000 (from 354 fewer to 637 more)
Pain-Severe	63 (2 studies) 24 hours	⨁⨁⊖⊖ LOW3 due to imprecision	RD 0.04 (-0.08 to 0.16)	Moderate	
				0 per 1000	40 more per 1000 (from 80 fewer to 160 more)
Pain-Very severe	33 (1 study) 24 hours	⨁⨁⨁⊖ MODERATE2 due to risk of bias	RD 0 (-0.15 to 0.15)	Moderate	
				0 per 1000	0 fewer per 1000 (from 150 fewer to 150 more)
Pain: patients with no pain	30 (1 study)	⨁⨁⨁⊖ MODERATE2 due to risk of bias	RR 5 (1.31 to 19.07)	Moderate	
				133 per 1000	532 more per 1000 (from 41 more to 1000 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
Pain: patients with pain	30 (1 study)	⨁⨁⊖⊖ LOW2,3 due to risk of bias, imprecision	RR 0.38 (0.18 to 0.81)	Moderate	
				867 per 1000	538 fewer per 1000 (from 165 fewer to 711 fewer)
Adverse events mean nausea score	206 (4 studies) 24 hours	⨁⨁⊖⊖ LOW1,3 due to inconsistency, imprecision			The mean adverse events mean nausea score in the intervention groups was 0.25 standard deviations lower (0.83 lower to 0.32 higher)
Adverse events mean Nausea score	245 (3 studies) 48 hours	⨁⨁⨁⊖ MODERATE3 due to imprecision			The mean adverse events mean ausea score in the intervention groups was 0.29 standard deviations lower (0.56 to 0.03 lower)
Adverse events: Nausea	2413 (29 studies)	⨁⨁⨁⨁ HIGH	RR 0.98 (0.88 to 1.10)	Moderate	
				305 per 1000	6 fewer per 1000 (from 37 fewer to 31 more)
Adverse events: Vomiting	1770 (24 studies)	⨁⨁⊖⊖ LOW3 due to imprecision	RR 1.17 (0.92 to 1.49)	Moderate	
				118 per 1000	20 more per 1000 (from 9 fewer to 58 more)
Adverse events: Nausea and vomiting	1949 (32 studies)	⨁⨁⨁⊖ MODERATE3 due to imprecision	RR 0.76 (0.66 to 0.88)	Moderate	
				300 per 1000	72 fewer per 1000 (from 36 fewer to 102 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
Adverse events: Respiratory depression	723 (6 studies)	⨁⨁⊖⊖ LOW3 due to imprecision	RR 1.05 (0.77 to 1.42)	Moderate	
				100 per 1000	5 more per 1000 (from 23 fewer to 42 more)
Additional opioid consumption	1148 (18 studies) <6 hours post-op	⨁⨁⊖⊖ LOW1 due to imprecision, inconsistency			The mean additional opioid consumption in the intervention groups was 0.91 standard deviations lower (1.35 to 0.47 lower)
Additional opioid consumption	2851 (44 studies) 24 hours post-op	⨁⨁⊖⊖ LOW1 due to inconsistency			The mean additional opioid consumption in the intervention groups was 1.25 standard deviations lower (1.63 to 0.86 lower)
Requiring additional opioid	485 (8 studies) 24 hours	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, inconsistency	RR 0.62 (0.38 to 0.994)	Moderate	
				571 per 1000	217 fewer per 1000 (from 6 fewer to 354 fewer)
Morphine injections (per patient)	245 (1 study)	⨁⨁⨁⊖ MODERATE2 due to risk of bias		The mean morphine injections (per patient) in the control groups was 2.52 injections	The mean morphine injections (per patient) in the intervention groups was 1.17 lower (1.31 to 1.03 lower)
PCA Fentanyl infusion rate	40 (1 study) <6 hours	⨁⨁⊖⊖ LOW2,3 due to risk of bias, imprecision		The mean pca fentanyl infusion rate in the control groups was 1.4	The mean pca fentanyl infusion rate in the intervention groups was 0.1 higher (0.24 lower to 0.44 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
PCA Fentanyl infusion rate	40 (1 study) 24 hours	⨁⨁⨁⨀ MODERATE2 due to risk of bias		The mean pca fentanyl infusion rate in the control groups was 0.6	The mean pca fentanyl infusion rate in the intervention groups was 0 higher (0.24 lower to 0.24 higher)
PCA use (morphine or morphine+ketamine)	278 (3 studies) 24 hours	⨁⨁⨀⨀ LOW1,2 due to risk of bias, inconsistency		The mean pca use (morphine or morphine+ketamine) in the control groups was 73.18 mg	The mean pca use (morphine or morphine+ketamine) in the intervention groups was 15.70 lower (35.84 lower to 4.44 higher)
Rescue analgesic interventions	410 (4 studies) 24 hours	⨁⨁⨁⨀ MODERATE2 due to risk of bias	RR 0.54 (0.4 to 0.72)	Moderate	
				455 per 1000	209 fewer per 1000 (from 127 fewer to 273 fewer)
Rescue Meperidine consumption	40 (1 study)	⨁⨁⨁⨀ MODERATE2 due to risk of bias		The mean rescue meperidine consumption in the control groups was 36 mg	The mean rescue meperidine consumption in the intervention groups was 14 lower (19.49 to 8.51 lower)
Requiring rescue NSAIDs	829 (7 studies)	⨁⨁⨁⨀ MODERATE2 due to risk of bias	RR 0.95 (0.8 to 1.13)	Moderate	
				500 per 1000	25 fewer per 1000 (from 100 fewer to 65 more)
Rescue NSAID requirement (mean times)	200 (1 study) 48 hours	⨁⨁⨁⨁ HIGH		The mean rescue nsaid requirement (mean times) in the control groups was	The mean rescue nsaid requirement (mean times) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
				2.325	0.75 lower (0.97 to 0.54 lower)
Requiring rescue propofol	80 (1 study)	⊕⊕⊕⊕ HIGH	RR 0.22 (0.11 to 0.44)	Moderate	
				800 per 1000	624 fewer per 1000 (from 448 fewer to 712 fewer)
Rescue propofol (mean dose)	80 (1 study)	⊕⊕⊕⊕ HIGH		The mean rescue propofol (mean dose) in the control groups was 1.6	The mean rescue propofol (mean dose) in the intervention groups was 1.2 lower (1.44 to 0.96 lower)
Rescue paracetamol needed	48 (1 study)	⊕⊕⊖⊖ LOW3 due to imprecision	RR 1.2 (0.42 to 3.41)	Moderate	
				208 per 1000	42 more per 1000 (from 121 fewer to 501 more)
Rescue Tramadol consumption	119 (1 study)	⊕⊕⊖⊖ LOW2,3 due to risk of bias, imprecision		The mean rescue Tramadol in the control group was 2mg	The mean rescue Tramadol in the intervention group was **3.08 higher** (0.12 lower to 6.27 higher)
Additional Metamizole	352 (1 study)	⊕⊕⊖⊖ LOW3 due to imprecision	RR 1.25 (0.6 to 2.59)	Moderate	
				68 per 1000	17 more per 1000 (from 27 fewer to 108 more)
Mean remfentanil dose (µg/kg-1/min-1)	50 (2 studies) 24 hours	⊕⊕⊕⊕ HIGH		The mean mean remfentanil dose (µg/kg-1/min-1) in the control groups was 0.3 µg/kg-1/min-1	The mean mean remfentanil dose (µg/kg-1/min-1) in the intervention groups was 0.04 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
					(0.07 lower to 0 higher)
Psychological distress - Delirium rating scale Scale from: 0 to 32. (Better indicated by lower)	90 (1 study) 2 days	⨁⨁⨁⊖ MODERATE3 due to imprecision		The mean psychological distress - delirium rating scale in the control groups was 3.1	The mean psychological distress - delirium rating scale in the intervention groups was 0.3 higher (0.06 to 0.54 higher)
Psychological distress Global assessment score Scale from: 0 to 4. (Better indicated by higher score)	20 (1 study) 3 days	⨁⨁⨁⊖ MODERATE3 due to imprecision		The mean psychological distress global assessment score in the control groups was 1.2	The mean psychological distress global assessment score in the intervention groups was 0.7 higher (0.11 lower to 1.51 higher)
Psychological distress Global assessment score Scale from: 0 to 4. (Better indicated by higher score)	20 (1 study) 7 days	⨁⨁⨁⊖ MODERATE3 due to imprecision		The mean psychological distress global assessment score in the control groups was 3	The mean psychological distress global assessment score in the intervention groups was 0.9 higher (0.31 to 1.49 higher)
Psychological distress - mini mental state examination Scale from: 0 to 30. Better indicated by higher score)	90 (1 study) 2 days	⨁⨁⨁⊖ MODERATE3 due to imprecision		The mean psychological distress - mini mental state examination in the control groups was 23	The mean psychological distress - mini mental state examination in the intervention groups was 0 higher (1.09 lower to 1.09 higher)
Psychological distress - Dysphoria	170 (3 studies)	⨁⨁⨁⊖ MODERATE3 due to imprecision	RD 0.07 (0.00 to 0.14)	Moderate	
				14 per 1000	70 more per 1000 (from 0 fewer to 140 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
Psychological distress – Severe depression	30 (1 study)	⨁⨁⊖⊖ LOW3 due to imprecision	Peto OR 0.14 (0.00 to 6.82)	67 per 1000	58 fewer per 1000 (from 67 fewer to 390 more)
Functional measure – Time to mobilisation (days)	242 (3 studies)	⨁⨁⊖⊖ LOW2,3 due to risk of bias, imprecision		The mean time to mobilisation in the control group was 4.2 days	The mean time to mobilisation in the intervention group was 0.36 lower (0.63 to 0.09 lower)
Functional measure – Mobilisation within 48 hours	30 (1study)	⨁⨁⊖⊖ LOW3 due to imprecision	RR 0.78 (0.39 to 1.54)	600 per 1000	132 fewer per 1000 (from 366 fewer to 324 more)
Functional measure: physical performance Scale from: 0 to 10. (Better indicated by higher)	28 (1 study) 4 days	⨁⨁⨁⨁ HIGH		The mean functional measure: physical performance in the control groups was 6.4	The mean functional measure: physical performance in the intervention groups was 2.4 higher (1.36 to 3.44 higher)
Functional measure (Time to 90 degree knee flexion) (better indicated by lower)	48 (1 study)	⨁⨁⨁⊖ MODERATE3 due to imprecision		The mean functional measusre (time to 90 degree knee flexion) in the control groups was 12.3 days	The mean functional measure (time to 90 degree knee flexion) in the intervention groups was 3.2 lower (5.52 to 0.88 lower)
Functional measure (time to maximal knee flexion) (better indicated by lower)	48 (1 study)	⨁⨁⨁⊖ MODERATE3 due to imprecision		The mean functional measusre (time to maximal knee flexion) in the control groups was 13.6 days	The mean functional measure (time to maximal knee flexion) in the intervention groups was 1.4 lower (4.21 lower to 1.41 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Opioid + Ketamine (95% CI)
Length of hospital stay	208 (4 studies)	⨁⨁⨁⨀ MODERATE1 due to inconsistency		The mean length of hospital stay in the control groups was 6.7 days	The mean length of hospital stay in the intervention groups was 0.84 lower (2.39 lower to 0.70 higher)
Length of stay in PACU	1014 (10 studies)	⨁⨁⨁⨁ HIGH		The mean length of stay in Pacu in the control groups was 78.3 minutes	The mean length of stay in Pacu in the intervention groups was 0.45 higher (0.25 lower to 1.16 higher)

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
4 No explanation was provided

Table 53: Evidence not suitable for GRADE analysis: IV Opioid and IV Ketamine compared to IV Opioid

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
Pain VAS < 6 hours	Adam 2005[2] (42)	Low	Reported in the graph Opioid group~2.3	Reported in the graph Ketamine+opioid group~2.3	n/a
	Aubrun 2008[14] (90)	Low	Reported in the graph Opioid group~1.8	Reported in the graph Ketamine and opioid group~1.8	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Aveline 2006[16] (69)	Low	median (25 th - 75th percentile) Opioid group – 4.6 (3.6-5.4)	median (25 th - 75th percentile) Ketamine and opioid group – 3.2 (2.2-3.7)	n/a
	Aveline 2009[15] (75)	Low	reported in the graph as median opioid group ~ 4.0	reported in the graph as median opioid and ketamine group~ 3.3;	n/a
	Cagla ozbakis akkurt 2009[32] (60)	High	Reported in the graph only; control group~4.4	Reported in the graph only Ketamine group~1.2;	n/a
	Darwish 2005[48] (60)	Low	reported in the graph control ~5.5	reported in the graph Ketamine group~3.7;	n/a
	Guillou 2003[80] (101)	High	reported in the graph only morphine group~4.0	reported in the graph only Ketamine group ~4.2,	n/a
	Han 2013[85] (40)	High	median control 3.5 (3-5)	median control 3.5 (3-5)	n/a
	Joly 2005[102] (75)	Low	reported in the graph only remifentanil~ 3.1	reported in the graph only Remifentanil+ketamine group ~2.2;	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Katz 2004[105] (143)	Low	There were no significant differences among the groups in VAS pain scores	There were no significant differences among the groups in VAS pain scores	P=0.05
	Kwok 2004[118] (135)	Low	Reported in the graph only Control~2.0	Reported in the graph only Pre-incision Ketamine~1.1 Post-incision Ketamine~2.0	n/a
	Lee 2014[125] (60)	Low	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.	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.	n/a
	Li 2016[129] (48)	High	reported in the graph only at 6 hours: Saline Group~4.3	reported in the graph only at 6 hours: Ketamine group~ 3.2	n/a
	Mathisen 1999[137] (60)	High	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	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	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
			post operatively were not statistically different. values presented in graph format	post operatively were not statistically different. values presented in graph format	
	Menigaux 2000[142] (45)	Low	Reported in the graph only control~3.3	Reported in the graph only Pre ~3.2; Post~2.8;	n/a
	Nesher 2008[163] (60)	High	Reported in the graph only control~4.5	Reported in the graph only ketamine~4	
	Nielsen 2017[166] (150)	Low	Reported in the graph only (no SD) Control – 4.8	Reported in the graph only (no SD) Ketamine group-4.6;	n/a
	Nistal-nuno 2014[168] (48)	Low	Reported in the graph only Control~0.5	Reported in the graph only Ketamine~ 1.5	n/a
	Nourozi 2010[169] (100)	Low	reported in the graph only Control group~4	reported in the graph only Ketamine group~ 4	n/a
	Parikh 2011[183] (60)	High	Reported in the graph only control group~ 8.5	Reported in the graph only Ketamine group~0.5	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Reza 2010[194] (60)	Low	Reported in the graph only control group~5.0	Reported in the graph only Ketamine group~5.0;	n/a
	Sahin 2004[202] (47)	High	Reported in the graph only control group~3	Reported in the graph only Ketamine group~5;	n/a
	Singh 2013[207] (80)	Low	Reported in graph (no SD) control~4.4	Reported in graph (no SD) Ketamine group~3.516 ;	n/a
	Stubhaug 1997[217] (20)	Low	Reported in the graph only control~2.5	Reported in the graph only Ketamine group~2.2;	n/a
	Yalcin 2012[253] (90)	High	reported in the graph control~2.5	reported in the graph control~2.5	n/a
	Yamauchi 2008[254] (202)	Low	Reported in the graph only control~2.5	Reported in the graph only Ketamine group(42µg)~2.5; Ketamine(83 µg)~2;	n/a
	Zakine 2008[257] (81)	Low	Reported in the graph; control~4.0	Reported in the graph Perioperative Ketamine group ~ 20; Intraoperative ketamine group ~ 2.5;	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
Pain VAS > 6 - 24 hours	Adam 2005[2] (42)	Low	Reported in the graph Opioid group~2.3	Reported in the graph Ketamine and opioid group~2.3	n/a
	Aubrun 2008[14] (90)	Low	Reported in the graph Opioid group~1.8	Reported in the graph Ketamine and opioid group~1.6	n/a
	Aveline 2006[16] (69)	Low	median (25 th - 75th percentile) Opioid group – 3.9 (32-41)	median (25 th - 75th percentile) Ketamine and opioid group – 2.9 (23-29)	n/a
	Aveline 2009[15] (75)	Low	reported in the graph as median Opioid group ~ 3.5	reported in the graph as median Opioid and ketamine group~ 2.3;	n/a
	Burstal 2001[31] (70)	High	median Morphine - 3	median ketamine - 2;	n/a
	Darwish 2005[48] (60)	Low	Reported in the graph control~4.4	Reported in the graph Ketamine~3.6	n/a
	Guillou 2003[80] (101)	High	reported in the graph only morphine group~4.0	reported in the graph only Ketamine group ~3.8,	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Han 2013[85] (40)	High	median control 3 (2-4.3)	median ketamine group 3 (2-4);	n/a
	Jaksch 2002[97] (30)	High	Reported in the graph only control~1.4	Reported in the graph only Ketamine group ~1;	n/a
	Joly 2005[102] (75)	Low	reported in the graph only remifentanil~ 3.0	reported in the graph only remifentanil~ 3.0	n/a
	Katz 2004[105] (143)	Low	There were no significant differences among the groups in VAS pain scores	There were no significant differences among the groups in VAS pain scores	p>0.05
	Kwok 2004[118] (135)	Low	Reported in the graph only Control~1.5	Reported in the graph only Pre-incision Ketamine~1.0 Post-incision Ketamine~1.5	n/a
	Li 2016[129] (48)	High	reported in the graph only at 24 hours: Saline Group~3.2	reported in the graph only at 24 hours: Ketamine group~2.5	n/a
	McKay 2007[138] (42)	Low	AUC (IQR) Placebo: 22.7 (12.6-38.1)	AUC (IQR) Ketamine: 24.6 (21.1-34.7);	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Menigaux 2000[142] (45)	Low	Reported in the graph only control~4.2	Reported in the graph only Pre ~32.4; Post~2.5;	n/a
	Nesher 2008[163] (60)	High	Reported in the graph only control~3.2	Reported in the graph only ketamine~3;	n/a
	Nielsen 2017[166] (150)	Low	Reported in the graph only (no SD) Control – 4.4	Reported in the graph only (no SD) Ketamine group-4.4;	n/a
	Nistal-nuno 2014[168] (48)	Low	Reported in the graph only Control~0.4	Reported in the graph only Ketamine~ 0.5;	n/a
	Nourozi 2010[169] (100)	Low	reported in the graph only Control group~1	reported in the graph only Ketamine group~ 1	n/a
	Parikh 2011[183] (60)	Low	Reported in the graph only; control group~ 2.0	Reported in the graph only Ketamine group~2.0;	n/a
	Roytblat 1993[199] (22)	high	reported in the graph only control group~0.5 (mean)	reported in the graph only ketamine group ~ 0.5 (mean);	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Singh 2013[207] (80)	Low	Reported in graph (no SD) control~3.75	Reported in graph (no SD) Ketamine group~3.68 ;	n/a
	Tang 2010[225] (40)	Low	median control 7.2(6.6-8.0)	median ketamine group 7.0(6.9-7.5);	n/a
	Weinbroum 2003[246] (245)	High	120 min after first morphine injection Morphine+saline~4	120 min after first morphine injection Morphine+ketamine group ~ 1.5	n/a
	Yalcin 2012[253] (90)	High	reported in the graph control~0.25	reported in the graph ketamine~0;	n/a
	Yamauchi 2008[254] (202)	Low	Reported in the graph only control~2.0	Reported in the graph only Ketamine group(42µg)~1.5; Ketamine(83 µg)~0.2;	n/a
	Zakine 2008[257] (81)		Reported in the graph control~3.0	Reported in the graph Perioperative ketamine ~ 1.0; Intraoperative ketamine group ~ 1.5;	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
Pain VAS day 2	Burstal 2001[31] (70)	High	Median Morphine - 2	Median Ketamine -2;	n/a
Pain VAS 96 hours	Kollender 2008[115]	Low	Pain was lower over 10 with opioid + ketamine compared to opioid only (values presented in graph format)	Pain was lower over 10 with opioid + ketamine compared to opioid only (values presented in graph format)	P<0.001
Pain NRS <6 hours	Bauchat 2011[23] (188)	Low	Median reported in the graph only Control~2.9	Median reported in the graph only Ketamine group ~2.8;	n/a
	Bilgen 2012[29] (140)	Low	Median(range) Control group - 1 (0-6)	Median(range) Ketamine group1(0.25mg) - 0 (0-5); Ketamine group2(0.5mg) - (0-6); Ketamine group3(1mg) - 0(0-8);	n/a
	Pacreu 2012[176] (22)	High	Median (IQR) Methadone: 7 (3.5-9)	Median (IQR) Methadone - Ketamine: 6 (4.25-8);	P=0.40
Pain(patient satisfaction VAS day 1	Burstal 2001[31] (70)	High	median (interquartile range) Morphine 8.5	median (interquartile range) Ketamine group 8 ;	n/a
Pain(patient satisfaction VAS day 2	Burstal 2001[31] (70)	High	median (interquartile range) Morphine 10	median (interquartile range) Ketamine group 8.5;	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
Pain VRS 60 min post operation	Unlugenc 2003[238] (90)	High	Reported in the graph only mean no SD morphine group ~2.7	Reported in the graph only mean no SD MOrphine +ketamine group~2.1;	n/a
Pain NRS 6-24 hours	Bauchat 2011[23] (188)	low	Median reported in the graph only Control~2.3	Median reported in the graph only Ketamine group ~2.2;	n/a
	Bilgen 2012[29] (140)	Low	Median(range) Control group - 0 (0-5)	Median(range) Ketamine group1(0.25mg) - 0 (0-4); Ketamine group2(0.5mg) - 0 (0-6); Ketamine group3(1mg) - 0(0-5);	n/a
	Ghazi-saidi 2002[77] (53)	Low	reported in the graph only control~6.2	reported in the graph only Ketamine~3.2,	n/a
	Kotsovolis 2015[117] (148)	Low	No SD Ketamine group - 4.2; Placebo group - 5.96	No SD Ketamine group - 4.2; Placebo group - 5.96	n/a
	Reza 2010[194] (60)	Low	Reported in the graph only control group~30	Reported in the graph only Ketamine group~35;	n/a
Pain VRS <6 hours	Garg 2016[73] (66)	Low	Median (interquartile range) Ketamine - 2(2-3); control 6(4.75-7)	Median (interquartile range) Ketamine - 2(2-3); control 6(4.75-7)	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Hasanein 2011[87] (60)	High	Median (IQR): 5 (4-8)	Median (IQR): 3 (1-2)	<0.05
	Kapfer 2005[104] (77)	High	reported in the graph only Ketamine~85%; Control group~78%	reported in the graph only Ketamine~85%; Control group~78%	n/a
	Li 2016[129] (48)	High	reported in the graph only at 6 hours: Saline Group~3.3	reported in the graph only at 6 hours: Ketamine group~ 3	n/a
	Reeves 2001[192] (71)	High	Reported in the graph only control ~2.1	Reported in the graph only control ~2.1	n/a
	Singh 2013[207] (80)	Low	Reported in graph (no SD) control~1.25	Reported in graph (no SD) Ketamine group~1.13 ;	n/a
	Unlugenc 2002[237] (66)	High	Median (range) tramadol 2 (1-3)	Median (range) tramadol+ketamine - 2(1-3);	n/a
	Unlugenc 2003[238] (90)	High	reported in median (range) Morphine group~ 2(1-3)	reported in median (range) Morphine +ketamine group~1 (1-2);	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Webb 2007[245] (120)	Low	Reported in the graph only control~2	Reported in the graph only Ketamine ~4	n/a
	Wilder-smith 1998[250] (45)	High	median Fentanyl group - 4(1-5)	median Ketamine group 4 (3-5);	n/a
Pain VRS 6-24 hours	Garg 2016[73] (66)	Low	Median (interquartile range) control 4(3-4.25)	Median (interquartile range) Ketamine - 2(1-3);	n/a
	Ilkjaer 1998[95] (52)	High	Median (interquartile range) ~4.1 (2.8-5.4)	Median (interquartile range) ~5.3 (4.5-6.7)	n/a
	Li 2016[129] (48)	High	reported in the graph only at 24 hours: Saline Group~2.2	reported in the graph only at 24 hours: Ketamine group~2	n/a
	Miziara 2016[147] (48)	Low	Median Control - 8.5	Median ketamine - 5.5	n/a
	Reeves 2001 [192] (71)	High	Reported in the graph only control ~1.2	Reported in the graph only Ketamine group~1.8;	n/a
	Roytblat 1993[199] (22)	High	VRS at 24 h reported in the graph Control~0.5	VRS at 24 h reported in the graph Ketamine~0.25;	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Singh 2013[207] (80)	Low	Reported in graph (no SD); control~4.4	Reported in graph (no SD) Ketamine group~1.3 ;	n/a
	Ulugenc 2002[237] (66)	High	Median (range) tramadol 1 (1-2)	Median (range) tramadol 1 (1-2)	n/a
	Unlugenc 2003[238] (90)	High	reported in median (range) Morphine group~ 1(1-2)	reported in median (range) Morphine +ketamine group~1 (1-2);	n/a
	Webb 2007[245] (120	Low	Reported in the graph only Ketamine ~1.5 control~1.5	Reported in the graph only Ketamine ~1.5 control~1.5	n/a
	Wilder-smith 1998[250] (45)	High	median Fentanyl group - 1(0-3)	median Ketamine group 2 (1-3);	n/a
Pain score arriving to PACU	Dullenkopf 2009[204] (120)	Low	Median (range) Control group 4 (0-9)	Median (range) Ketamine(0.15mg/kg) 3(0-10); ketamine(0.5mg/kg) 4(0-9);	n/a
	Lenzmeier 2008[126] (22)	High	Median VAS (0-100) Opioid: 66	Median VAS (0-100) Ketamine: 24;	

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
Postoperative pain 0-20 hours	Ayoglu 2005[17] (40)	High	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.		P<0.05
Pain intensity (Spid-summed pain intensity difference)	Beaudoin 2014[24] (60)	Low	Median IQR Control 4.0(1.8 - 6.5)	Median IQR Group(0.15mg) - 7(4.3 - 10.8); Group(0.3mg) 7.8(4.8 - 12.8	n/a
Pain area under curve	Duale 2009[59] (86)	High	Area under curve Opioid: 88 ± 34	Area under curve Ketamine: 73 ± 40;	p value = 0.039
Pain VAS at discharge	Suzuki 1999[221] (140)	Low	Reported in the graph only Control~40	Reported in the graph only Ketamine~ 29	n/a
Median pain thresholds on the stump day 3 postop	Hayes 2004[90] (45)	High	median pain thresholds on the stump Control group - 5.88 units (IQR 1.07)	median pain thresholds on the stump Ketamine group - 5.18 units (IQR 1.23)	P=0.12
Median pain thresholds on the stump day 3 postop	Hayes 2004[90] (45)	High	median pain thresholds on the stump Control - 5.07 (IQR 0.72)	median pain thresholds on the stump Ketamine - 5.18 (IQR 0.81)	P=0.37
Pain scale 0-2, <6 hours	Murdoch 2002[161] (42)	High	Reported in the graph as proportions (%) 4 hours - score 0 (Ketamine group ~65; control ~70%)	Reported in the graph as proportions (%) 4 hours - score 0 (Ketamine group ~65; control ~70%)	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
			4 hours - score 1 (Ketamine group ~25%; control ~30%) 4 hours - score 2 (Ketamine group ~10%; control ~0%)	4 hours - score 1 (Ketamine group ~25%; control ~30%) 4 hours - score 2 (Ketamine group ~10%; control ~0%)	
Pain scale 0-2, 24hours	Murdoch 2002[161] (42)	High	Reported in the graph as proportions (%) 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%)	Reported in the graph as proportions (%) 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%)	n/a
Pain - number of occasions pain ≥2 was recorded	Murdoch 2002[161] (42)	High	26/21	25/21	n/a
Pain tactile pain threshold 24 hours post op	Song 2014[212] (75)	Low	Reported in the graph only Group L~120; Group H ~75	Reported in the graph only Ketamine group ~120; Group L~120; Group H ~75	n/a
Time needed to active 90 degree knee flexion	Adam 2005[2] (42)	Low	Median (IQR) (25% - 75%) Opioid - 12(8-45)	Median (IQR) (25% - 75%) Ketamine - 7(5-11)	n/a
Cumulative morphine consumption <6	Aveline 2006[16] (69)	Low	Reported in the graph only Opioid group ~8	Reported in the graph only Ketamine and opioid	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
hours				group~2.5	
	Darwish 2005[48] (60)	Low	Median (range) Control - 21 (15-29)	Median (range) Ketamine - 16 (9-22);	n/a
	Gillies 2007[78] (41)	Low	Morphine mean - 14.4, 95% CI 10-18.9;	Ketamine + morphine group mean - 8.9 mg, 95% CI 5.6-12.1;	P=0.08
	Guignard 2002[79] (50)	Low	Median (interquartile range) Control 26 (19-36)	Median (interquartile range) Ketamine 21 (10-23);	n/a
	Guillou 2003[80] (101)	High	reported in the graph only morphine group~12	reported in the graph only Ketamine group ~5mg,	n/a
	Jaksch 2002[97] (30)	High	median amount control group-12	median amount Ketamine group - 12	n/a
	Kotsovolis 2015[117] (148)	Low	reported in the graph only (no SD) Placebo group ~12	reported in the graph only (no SD) Ketamine group ~14;	n/a
	Lenzmeier 2008[126] (22)	High	Median Opioid: 6.0mg	Median Ketamine: 3.8mg;	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Nistal-nuno 2014[168] (48)	Low	Reported in the graph only Control~12 mg	Reported in the graph only Control~12 mg	n/a
	Reza 2010[194] (60)	Low	Reported in the graph only control group~9	Reported in the graph only Ketamine group~4.8;	n/a
	Unlugenc 2003[238] (90)	High	reported in median (range) Morphine +ketamine group~14.1 (12-17); Morphine group~ 14.9(14-17)	reported in median (range) Morphine +ketamine group~14.1 (12-17); Morphine group~ 14.9(14-17)	n/a
Cumulative morphine consumption 6 -24 hours	Aveline 2006[16] (69)	Low	Reported in the graph only Opioid group ~15	Reported in the graph only Ketamine and opioid group~7.5	n/a
	Ayoglu 2005[17] (40)	High	Values provided in graph format. No significant difference between groups at 4 or 20 hours.		n/a
	Darwish 2005[48] (60)	Low	Median (range) Control - 38 (20-48)	Median (range) Ketamine - 21 (13-30);	n/a
	Duale 2009[59] (86)	High	Median (IQR) Opioid: 41mg (32-59)	Median (IQR) Ketamine: 37mg (24-49);	p value = 0.068
	Edwards 1993[62] (40)	High	Mean (range) control group - 47.7(16-99);	Mean (range) ketamine 5 - 35.1(15-64); ketamine10 - 43.2 (18-87);	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
				ketamine20-36.3(18-55)	
	Gillies 2007[78] (41)	Low	Morphine mean - 14.0, 95% CI 7-18;	Ketamine + morphine group mean - 9 mg, 95% CI 3.5-14;	P=0.08
	Guignard 2002[79] (50)	Low	Median (interquartile range) Control 69 (41-87)	Median (interquartile range) Ketamine 46 (34-58);	n/a
	Guillou 2003[80] (101)	High	reported in the graph only morphine group~50	reported in the graph only Ketamine group ~38,	n/a
	Hayes 2004[90] (45)	High	Median morphine Control 42 IQR 47	Median morphine Ketamine 44 mg, IQR 32	P=0.61
	Jaksch 2002[97] (30)	High	median amount; Control group 29 mg	median amount Ketamine group 39 mg;	n/a
	Kotsovolis 2015[117] (148)	Low	reported in the graph only (no SD) Placebo group ~20	reported in the graph only (no SD) Ketamine group ~22;	n/a
	McKay 2007[138] (42)	Low	Median (IQR) Placebo: 76mg (35-198)	Median (IQR) Ketamine: 120mg (51-208);	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Michelet 2007[126] (50)	Low	Reported in the graph only Control~30	Reported in the graph only Ketamine~25;	n/a
	Nistal-nuno 2014[168] (48)	Low	Reported in the graph only Control~45 mg	Reported in the graph only Ketamine~ 48 mg;	n/a
	Reza 2010[194] (60)	Low	Reported in the graph only control group~2.9	Reported in the graph only Ketamine group~3;	n/a
	Roytblat 1993[199] (22)	High	mean consumption of morphine (no SD) control group 48.7 mg	mean consumption of morphine (no SD) Ketamine group 29.5 mg,	n/a
	Stubhaug 1997[217] (20)	Low	reported on the graph only control 65	reported on the graph only Ketamine~60,	n/a
	Unlugenc 2003[238] (90)	High	reported in median (range) Morphine group~ 49.0(46-51)	reported in median (range) Morphine +ketamine group~46.5 (43-51);	n/a
	Weinbroum 2003[246] (245)	High	Mean no SD morphine group - 1.21	Mean no SD Morphine + ketamine group - 0.42;	n/a
	Zakine 2008[257] (81)	Low	Median (IQR) control 50 mg iqr-21 p<0.005	Median (IQR) Peri group - 27mg, IQR19; Intra group 48 mg (41.5);	p<0.005

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
				p<0.005	
Cumulative morphine consumption at 48 hours	Joly 2005[102] (75)	Low	median Small dose remifentanil 68 (50-91) mg Large dose remifentanil 86 (59-109) mg	median Large remifentanil + ketamine 62 (48-87)	n/a
Cumulative morphine consumption at 72 hours	Hayes 2004[90] (45)	High	Median morphine Control 72 mg IQR 100	Median morphine Ketamine group 118 mg IQR 86	P=0.34
Mean total morphine consumption 24 hours	Kotsovolis 2015[117] (148)	Low	Mean (no SD) Placebo group - 20.29	Mean (no SD) Ketamine group - 22.38;	n/a
Mean total morphine consumption 24 hours	Lo 2008[131] (30)	Low	Mean morphine consumption no SD Morphine group - 129 mg	Mean morphine consumption no SD Ketamine+morphine group 60 mg (also 60 mg ketamine)	n/a
Rescue morphine consumption	Nielsen 2017[166] (150)	Low	Median(quartiles) control 15(7-26)	Median(quartiles) Ketamine group - 13(3-26);	n/a
Cumulative ibuprofen dose 24 hours	Bauchat 2011[23] (188)	Low	Median (interquartile range) Control 3600(2400 -4200)	Median (interquartile range) Ketamine group - 3600(1200-4200);	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
Cumulative acetaminophen/hydrocodone tablets 24 hours	Bauchat 2011[23] (188)	Low	Median (interquartile range) Control 1(0 -4)	Median (interquartile range) Ketamine group - 2(1-4);	n/a
Amount of rescue analgesia (morphine equivalents)	Beaudoin 2014[24] (60)	Low	Median Ketamine1 - 5.4; ketamine2 - 4.3;	Median Ketamine1 - 5.4; ketamine2 - 4.3;	n/a
Dose of rescue Pethidine	Nourozi 2010[169] (100)	Low	reported in the graph only at 6 hours Control group~4mg at 19 hours Control group~0	reported in the graph only at 6 hours Ketamine group~ 1mg at 19 hours Ketamine group~ 0	n/a
Total fentanyl consumption <6 hours	Yamauchi 2008[254] (202)	Low	Reported in the graph only control~9	Reported in the graph only Ketamine group(42µg)~8; Ketamine(83 µg)~6;	n/a
Total fentanyl consumption <6-24 hours	Yamauchi 2008[254] (202)	Low	Reported in the graph only control~16	Reported in the graph only Ketamine group(42µg)~15; Ketamine(83 µg)~12;	n/a
PONV	Hadi 2009[81] (40)	High	no differences were noted in the incidence of pruritis, postoperative nausea and vomiting in the two groups.	no differences were noted in the incidence of pruritis, postoperative nausea and vomiting in the two groups.	n/a

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
	Nourozi 2010[169] (100)	Low	reported in the graph only Control group~8 at 24 hours Control group~1	reported in the graph only at 6 hours Ketamine group~ 3 at 24 hours Ketamine group~ 0	n/a
Total dose of Remifentanil (mg) 24 hours	Leal 2015[124] (56)	Low	Mean (range; minimal value - maximal value) control group - 3.1(1.5 - 7.5)	Mean (range; minimal value - maximal value) Ketamine group - 3.7 (1.2-7.2);	n/a
Meperidine consumption 4h post op	Mathisen 1999[137] (60)	High	There was no significant difference between groups in meperedine consumption at 4 hours, 24 hours or 7 days post-op	There was no significant difference between groups in meperedine consumption at 4 hours, 24 hours or 7 days post-op	n/a
Length of hospital stay	McKay 2007[138] (42)	Low	Median (IQR) Placebo: 6.7 (9-10)	Median (IQR) Ketamine: 7 days (7-8)	n/a
Methadone consumption <6 hours post op	Pacreu 2012[176] (22)	Low	Median (IQR) Methadone: 4 (0.5 - 5.5)	Median (IQR) Methadone - Ketamine: 3.5 (0.5 - 5.5) ;	P=1
Methadone consumption <24 hours post op	Pacreu 2012[176] (22)	Low	Median (IQR) Methadone: 15 (9.65-17.38)	Median (IQR) Methadone - Ketamine: 3.43 (1.9-6.5	P<0.001

Outcome	Study (no. of participants)	Risk of bias	Opioid results	Opioid and Ketamine results	*P* value
Mean number of analgesic doses given in 24 hours	Singh 2013[207] (80)	Low	Reported in graph (no SD) control~7.35	Reported in graph (no SD) Ketamine group~4.416 ;	n/a
Nausea score (0-none, 2 – severe) 24 hours	Reeves 2001[192] (71)	High	Median(10th to 90th percentile) control group 0 (0-1)	Median(10th to 90th percentile) Ketamine group - 0 (0-1);	n/a
	Webb 2007[245] (120	Low	Median (range) control-0(0-2)	Median (range) Ketamine- 1(0-2)	n/a
Nausea score (0-none, 2 – severe) 48 hours	Reeves 2001[192] (71)	High	Median(10th to 90th percentile) control group 0 (0-2)	Median(10th to 90th percentile) control group 0 (0-2)	n/a
	Webb 2007[245] (120)	Low	Median (range) control-0(0-2)	Median (range) Ketamine- 0(0-2)	n/a

See appendices for full GRADE tables.

4.4 Economic evidence

4.4.1 Included studies

No health economic studies were included.

4.4.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendices.

4.4.3 Unit costs

The average daily costs of ketamine and intravenous opioids are provided in Table 54Table 49 to help aid consideration of cost effectiveness. A breakdown of these costs is provided in the appendices for the pain evidence review.

Table 54: Average daily costs of ketamine and opioids

Analgesic	Average daily cost per person (range)[(a)]
Intravenous ketamine	£6.06
Intravenous opioid	£4.92 (£3.77 – £6.07)
Intravenous opioid & ketamine	£7.75 (£6.60 - £8.90)

Sources: British National Formulary, Accessed September 2019[101]; Electronic market information tool (eMIT), Accessed September 2019[43]

(a) Costs include disposable costs, see the appendices for the pain evidence review for a breakdown of these costs.

4.4.4 Other calculations

Calculations based on QALY thresholds are provided below to help aid consideration of cost effectiveness.

Table 55: EQ-5D scores using the valuation set with severe versus moderate pain

EQ5D score assumptions[(a)]	EQ5D score at baseline	New EQ-5D score after pain relief	Difference
Patients experience severe pain and score 3 on pain and 2 on everything else After pain relief their pain score changes to 2	-0.016	0.503	0.519
Patients score 3 on all of the dimensions and after pain relief their pain score changes to 2	-0.594	-0.331	0.263

(a) Based on the EQ-5D-3L which comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems and extreme problems.

Using an average cost of ketamine of £6.06 and a threshold of £20,000 per QALY, the difference in QALYs needed for ketamine to be considered cost-effective is:

£6.06/£20,000 = 0.000303 QALYs

QALY threshold calculations:

- If we take the difference in EQ-5D from scoring a 3 in pain to a 2 in pain calculated above(0.519) based on the assumption all other domains would have a score of 2.
- And assume the time frame is 6 hours
- This results in ketamine having an additional 0.00036 QALYs
- This is bigger than the 0.000142 QALYs required to ensure that ketamine is cost-effective

- If we use the worst case scenario and take the difference in EQ-5D from scoring a 3 in pain to a 2 in pain (with all other dimensions also scored a 3)

- And assume the time frame is 6 hours
- This results in ketamine having an additional 0.00018 QALYs, which is just below the amount required for it to be considered cost-effective at a £20,000 per QALY threshold.

This shows that a reduction in pain leads to a bigger change in utility when other domains are scored lower and in this case ketamine would be considered cost effective.

4.5 Evidence statements

4.5.1 Clinical evidence statements

No outcomes were reported for health related quality of life or the following important outcomes;symptom scores and hospital readmission.

Opioid plus Ketamine versus Opioid

Pain

Twenty five studies showed a clinically important benefit with opioid plus ketamine in pain at six hours post-operatively compared to opioid (25 studies, n=1505, very low quality evidence)

Thirty one studies showed no clinically important difference between opioid plus ketamine and opioid alone in pain at twenty four hours post-operatively (31 studies, n=2355, very low quality evidence)

One study showed no clinically important difference between opioid plus ketamine and opioid alone for no pain at four hours postoperatively (1 study, n=33, modereate quality evidence)

One study showed no clinically important difference between opioid plus ketamine and opioid for mild pain at 4 hours (1 study, n=33, moderate quality evidence)

One study showed a clinically important benefit with opioid plus ketamine in fewer episode of moderate or severe pain at four hours (1 study, n=33, very low quality evidence)

One study showed no clinically important difference between opioid plus ketamine and ketamine for very severe pain at four hours (1 study, n=33, very low quality evidence)

Two studies showed a clinically important benefit with opioid plus ketamine in the number of people with no pain twenty four hourscompared to opioid alone (2 studies, n=63, very low quality evidence)

Two studies showed no clinically important difference between opioid plus ketamine and opioid for people with mild pain at twenty four hours (2 studies, n=63, low quality evidence)

One study showed a clinically important benefit with opioid plus ketamine for people with moderate pain at twenty four hours (2 studies, n=63, very low quality evidence)

Two studies showed no clinically important difference between opioid plus ketamine and opioid for people with severe pain at twenty four hours (2 studies, n=63, low quality evidence)

Two studies showed no clinically important difference between opioid plus ketamine and opioid for people with very severe pain at twenty four hours (2 studies, n=63, moderate quality evidence)

One study showed a clinically important benefit with opioid plus ketamine in the cases of people experiencing post-operative pain compaired to opioid alone (1 study, n=30, moderate quality evidence)

Adverse events

Four studies showed no clinically important difference between opioid plus ketamine and opioid in mean nausea score at twenty four hours (4 studies, n=206, low quality evidence)

Three studies showed no clinically important difference between opioid plus ketamine and opioid in mean nausea score forty eight hours (3 studies, n=245, moderate quality evidence)

Twenty nine studies showed no clinically important difference between opioid plus ketamine and opioid in cases of nausea (29 studies, n=2413, high quality evidence)

Twenty four studies showed no clinically important difference between opioid plus ketamine and opioid in cases of vomiting (24 studies, n=1770, low quality evidence)

Thirty two studies showed no clinically important difference between opioid plus ketamine and opioid in cases of nausea and vomiting (32 studies, n=1949, moderate quality evidence)

Six studies showed no clinically important difference between opioid plus ketamine and opioid in cases of respiratory depression (6 studies, n=723, moderate quality evidence)

Rescue medication

Eighteen studies showed a clinically important benefit with opioid plus ketamine in opioid consumption at six hours post-operatively compared to opioid alone (18 studies, n=1148, low quality evidence)

Fourty four studies showed a clinically important benefit with opioid plus ketamine in opioid consumption at twenty four hours post-operatively compared to opioid alone (44 studies, n=2851, low quality evidence)

Eight studies showed a clinically important benefit with opioid plus ketamine in patients requiring additional opioid at twenty four hours post-operatively compared to opioid alone (8 studies, n=485, low quality evidence)

One study showed a clinically important benefit with opioid plus ketamine in morphine injections compared to opioid alone (1 study, n=245, moderate quality evidence)

One study found no clinically important difference between opioid plus ketamine and opioid in PCA fentanyl infusion rate at six or twenty four hours postoperatively (n=40 low to moderate quality evidence)

Three studies found no clinically important difference between opioid plus ketamine and opioid in PCA (morphine or morphine plus ketamine) use (3 studies, n=278, low quality evidence)

Four studies showed a clinically important benefit with opioid plus ketamine in the number of rescue analgesic interventions compared to opioid alone (4 studies, n=410, moderate quality evidence)

One study showed a clinically important benefit with opioid plus ketamine in the number of rescue meperidine consumed compared to opioid alone (n=40, moderate quality evidence)

Seven studies showed no clinically important difference between opioid plus ketamine and opioid for rescue NSAIDs (7 studies, n=829, moderate quality evidence)

One study found a clinically important benefit of opioid plus ketamine for mean requirement of rescue NSAID compared to opioid alone (1 study, n=200, high quality evidence)

One study showed a clinically important benefit with opioid plus ketamine in people requiring rescue propofol compared to opioid alone (1 study, n=80, high quality evidence)

One study showed no clinically important difference between opioid plus ketamine and opioid in people requiring rescue paracetamol (1 study, n=48, low quality evidence)

One study showed no clinically important difference between opioid plus ketamine and opioid in people requiring rescue tramadol (1 study, n=119, low quality evidence)

One study showed no clinically important difference between opioid plus ketamine and opioid in people requiring rescue metamizole (1 study, n=352, low quality evidence)

Two studies found no clinically important difference between opioid plus ketamine and opioidfor mean remifentanil dose required (2 studies, n=50, high quality evidence)

Psychological distress and well-being

One study showed no clinically important differencebetween opioid plus ketamine and opioid for delirium (1 study, n=90, moderate quality evidence)

One study found no clinically important difference between opioid plus ketamine and opioid for psychological distress (global assessment scale) (1 study, n=20, moderate quality evidence)

One study showed no clinically important difference between opioid plus ketamine and opioid for psychological distress (mini mental state examination) (1 study, n=90, modertate quality evidence)

Three studies found no clinically important difference between opioid plus ketamine and opioid for dysphoria (3 studies, n=170, moderate quality evidence)

One study reported no difference between opioid plus ketamine and opioid for severe depression (1 study, n=30, low quality evidence)

Functional measures

Three studies found a clinically important benefit with opioid plus ketamine for mean time to mobilisation compared to opioid alone (3 studies, n=30, low quality evidence)

One study found a clinically important harm with opioid plus ketamine for the number of people mobilised within 48 hours compared to opioid alone (1 study, n=30, low quality evidence)

One study found a clinically imoprtant benefit with opioid plus ketamine on physical performance scale postoperatively compared to opioid alone (1 study, n=28, low quality evidence)

One study found a clinically important benefit with opioid plus ketamine for time to 90 degrees knee flexion, but no difference for time to maximum knee flexion postoperatively compared to opioid alone (1 study, n=48, moderate quality evidence)

Length of stay

Four studies showed no clinically important difference between opioid plus ketamine and opioid alone for length of hospital stay (4 studies, n=208, moderate quality evidence)

Tenstudies showed no clinically important difference between opioid plus ketamine and opioid alone for length of PACU stay (10 studies, n=1014, high quality evidence)

Evidence not suitable for GRADE analysis

Pain

Twenty seven studies reported pain within the first 6 hours of surgery. Results were mixed, showing a benefit of ketamine or no difference between groups. (27 studies, n=1996, low to high risk of bias)

Twenty seven studies reported pain at 6 to 24 hours from surgery. Results were mixed, showing a benefit of ketamine or no difference between groups. (27 studies, n=2243, low to high risk of bias)

Rescue medication

Eleven studies reported opioid consumption within 6 hours of surgery. Results were mixed, showing a benefit of ketamine or no difference between groups. (11 studies, n=719, low to high risk of bias)

Twenty studies reported opioid consumption at 6 to 24 hours of surgery. Results were mixed, showing a benefit of ketamine or no difference between groups. (20 studies, n=1328, low to high risk of bias)

Adverse events

Four studies reported no significant difference post-operative nausesa or vomiting (4 studies, n=331, low to high risk of bias)

Length of stay

One study showed no diference in length of hospital stay (1 study, n=42, low quality evidence)

4.5.2 Health economic evidence statements

- No relevant economic evaluations were identified.

5 Neuropathic nerve stabilisers

5.1 Review question: What is the clinical and cost effectiveness of neuropathic nerve stabilisers in managing acute post-operative pain?

5.2 PICO table

For full details see the review protocol in appendices.

Table 56: PICO characteristics of review question

Population	Adults (18 years and older) who have undergone surgery.

Interventions	• Opioids +
	  ○ pregabalin
	  ○ gabapentin
	  ○ nortriptylline
	  ○ amitriptyline

Comparisons	• Opioids + placebo • Each other

Outcomes	CRITICAL:
	• health-related quality of life
	• pain reduction
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• amount of additional medication use
	  ○ ≤ 6 hours post op
	  ○ > 6 hours- 24 hours post op
	• adverse events (including respiratory depression, nausea, vomiting, sedation, postural hypotension, antimuscarinic/ anticholinergic side effects)
	IMPORTANT:
	• psychological distress and mental well-being
	• symptom scores
	• functional measures
	• length of stay in hospital

Study design	Randomised controlled trials and systematic reviews of randomised controlled trials.

5.3 Clinical evidence

5.3.1 Included studies

Fifty-nine randomised controlled trials were included in the review;[1, 4, 5, 8, 11, 21 25, 41, 55, 57, 61, 64, 76, 88, 91, 93, 106-110, 112, 121, 127, 134-136, 144, 146, 148, 149, 152, 164, 175, 178-182, 189, 196, 203, 206, 210, 213, 214, 220, 223, 232-234, 240, 241, 249, 256, 259 86 63 177] these are summarised in Table 57 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 58).

See appendices for the study selection flow chart, study evidence tables, forest plots and GRADE tables.

5.3.2 Excluded studies

See the excluded studies list in appendices.

5.3.3 Summary of clinical studies included in the evidence review

Table 57: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Abdelmageed 2010[1]	**Gabapentin**: 1200mg oral gabapentin 2 hours before surgery. 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)** **Placebo**: Placebo given 2 hours before surgery. 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)**	Patients aged 18 - 35 old, ASA I - II Tonsillectomy under general anaesthesia Age - Mean (SD): Gabapentin: 31.4 ± 7.7; Placebo 29.8 ± 6.5 Saudi Arabia	• Pain score • Dose of additional opioid • Adverse events	
Agarwal 2008[4]	**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. 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. **(n=30)**	Patients ASA I and II, undergoing laparoscopic cholecystectomy under general anaesthesia. Age - Mean (range): Pregabalin: 46.6 (25–76); Placebo: 44.6 (22–69). India	• Pain scores • Dose of additional opioid • Adverse events	Pain scores, dose of additional opioid and sedation score given as median

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo: Placebo 1h before the induction of anesthesia with sips of water by a staff nurse who was not involved in the study. 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. **(n=30)**			
Ajori 2012[5]	**Gabapentin**: Two 300 mg capsules of gabapentin. The medication was given to the patients about 1 h before induction of anesthesia..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. **(n=70)** **Placebo**: Patients were given two placebo capsules. The medication was given to the patients about 1 h before induction of anesthesia. When	Candidates for abdominal hysterectomy; ASA class I and II, nonmalignant status (benign gynecologic disease), under general anesthesia, and body mass index (BMI) of 20–30 kg/m2 Age - Mean (SD): Gabapentin: 49.2 ± 7.1; Placebo: 48.3 ± 8.9. Iran	• Pain scores • Dose of additional opioids • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	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 **(n=70)**			
Alimian 2012[11]	**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 operation injecting of opioids was prohibited. For the patients whose pain intensity exceeded three on VAS measurement, 25 mg pethedine was administered intramuscularly and documented, **(n=40)** **Placebo:** 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	Patients aged 18 to 60 years old, being a volunteer to undergo Dacryocysto-rhinostomy Surgery, an ASA status of I or II Age - Mean (SD): Pregabalin: 41.1 ± 14.1; Placebo: 45.4 ± 15.7. Iran	• Pain scores • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	administration. Concurrent medication/care: For the patients whose pain intensity exceeded three on VAS measurement, 25 mg pethedine was administered intramuscularly and documented. **(n=40)**			
Al-Mujadi 2006[8]	**Gabapentin:** 1200mg of gabapentin two hours before surgery. 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. **(n=41)** **Placebo**: placebo capsules two hours before surgery. 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. **(n=37)**	ASA I or II scheduled for elective thyroid surgery under general anaesthesia Age - Mean (SD): Gabapentin: 45±13; Placebo: 49±15. United Arab Emirates	• Pain scores • Dose of additional opioids • Adverse events	
Balaban 2012[21]	**Pregabalin**: Received pregabalin (150 mg or 300 mg) orally one hour	Patients over 18 years of age and scheduled for laparoscopic	• Dose of additional opioids • Adverse events	Intervention groups with different dosages (150mg and 300mg) were combined as there are no

Study	Intervention and comparison	Population	Outcomes	Comments
	before surgery. None of the patients received other premedication. If a VAS score was 5 or more, intravenous fentanyl 25 µg was given and repeated if required. **(n=60)** **Placebo**: oral placebo one hour before surgery. If a VAS score was 5 or more, intravenous fentanyl 25 µg was given and repeated if required. **(n=30)**	cholecystectomy Age - Mean (SD): Pregabalin: 53.6 ± 13.36; Placebo 51.4 ± 15.7. Turkey		pre-defined dosages for perioperative care
Behdad 2012[25]	**Gabapetin**: gabapentin the night before surgery and 300 mg gabapentin (one capsule) two hours before surgery. Opioids used as rescue medication, type of opioid used not specified **(n=30)** **Placebo:** In the Placebo group, patients got one capsule of multi-vitamin two hours before surgery. Opioids used as rescue medication, type of opioid used not specified **(n=31)**	Patients > 20 years old and over 40 kg of weight undergoing total abdominal hysterectomy under general anaesthesia Age - Mean (SD): Gabapentin: 45.86 ± 4.06; Placebo: 48.16 ± 4.48. Iran	• Pain scores • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
Clarke 2013[41]	**Gabapentin**: Gabapentin 1,200 mg administered 2.5 hours before surgery. Results show patients received Fentanyl (µg) Morphine (mg) but not dosage information given. **(n=25)** **Placebo:** Placebo administered 2.5 hours before surgery. Results show patients received Fentanyl (µg) Morphine (mg) but not dosage information given. **(n=25)**	Patients 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. Age - Mean (SD): Gabapentin: 41.6±6.6; Placebo: 41.8±6.8. Canada	• Pain scores • Anxiety score • McGill pain score • Dose of additional opioid	Pain scores, Anxiety score, McGill pain score all given as median values
Dierking 2004[55]	**Gabapentin**: Oral gabapentin 1200 mg 1 h before surgery, followed by oral gabapentin 600 mg 8, 16 and 24 h after the initial dose. 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	Women aged 18—75 years, scheduled for elective total or subtotal abdominal hysterectomy with or without salpingo-oophorectomy Age - Median (range): Gabapentin: 46 (26—73); Placebo: 48 (36—62). Denmark	• Adverse events	Somnolence given as a median value

Study	Intervention and comparison	Population	Outcomes	Comments
	on patient request. No other medications were administered during the 24-h observation period. **(n=40)** **Placebo:** Receive oral placebo 1 h before surgery, followed by placebo 8, 16 and 24 h after the initial dose. 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. **(n=40)**			
Dirks 2002[57]	**Gabapentin**: 1,200 mg oral gabapentin 1 h before surgery and 0.125 mg sublingual triazolam. patient-controlled intravenous morphine, 2.5-mg bolus, 10 min lock-out time. Additional	Women aged 18–75 yr who were scheduled for unilateral radical mastectomy with axillary dissection were eligible for the study. Age - Mean (range): Gabapentin: 61 (54–67);	• Pain scores • Dose of additional opioid • Adverse events	Pain scores and dose of additional opioid given as median values

Study	Intervention and comparison	Population	Outcomes	Comments
	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 **(n=35)** **Placebo:** Identical placebo 1 h before surgery and 0.125 mg sublingual triazolam. 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. **(n=35)**	Placebo: 60 (52–69). Denmark		
Durmus 2007[61]	**Gabapentin**: Gabapentin 1200mg 1 hour prior to the induction of	Patients ASA I–II, aged ≥18 who were scheduled for elective total abdominal hysterectomy under general	• Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	anaesthesia . 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. **(n=25)** **Placebo:** Placebo capsules 1 hour before the induction of anesthesia. 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	anaesthesia in the Gynaecology and Obstetrics Department who could operate a patient-controlled analgesia (PCA) device Age - Mean (SD): Gabapentin: 48 ± 7; Placebo: 48 ± 7 Turkey		

Study	Intervention and comparison	Population	Outcomes	Comments
	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. **(n=25)**			
Eidy 2017[63]	**Gabapentin:** Patients were given Gabapentin 800mg one hour before surgery given 1 hour before surgery (n=36) **Pregabalin:** Patients were given 150mg of pregabalin orally, one hour before surgery (n=36) **Placebo:** Patients in the placebo group did not receive Pregabalin or Gabapentin preoperatively (n=36)	Patients aged between 20 - 60 ASA I or II undergoing laparoscopic cholecystectomy Mean age (SD): Gabapentin:44.0 ± 9.5; Pregabalin:43.1 ± 1.1; Placebo: 45.3 ± 9.3 Iran	• Opioid consumption • Adverse events	
Eman 2014[64]	**Pregabalin:** 150 mg of oral pregabalin given 60 minutes prior to the surgery. 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	Patients >18-60 years, ASA I-II scheduled for total abdominal hysterectomy surgery under general anaesthesia Age - Mean (SD): Pregabalin: 43.45 ± 11.56; Placebo: 42.15 ± 11.12	• Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. **(n=20)** **Placebo:** oral placebo capsule given 60 minutes prior to the surgery. 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 times **(n=20)**	Turkey		
Ghafari 2009[76]	**Gabapentin:** 300mg Gabapentin at 10pm the night before surgery and 1 hour before surgery. Postoperative IV analgesia was provided through a PCA. The PCA pump	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	• Pain scores • Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. **(n=33)** **Placebo:** Placebo given at 10pm the night before surgery and 1 hour before surgery. 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. **(n=33)**	problem Age - Mean (SD): gabapentin: 44.65 ± 1.31; Placebo: 44.55 ± 1.12 Iran		
Hanoura 2018[86]	**Gabapentin:** 600mg gabapentin 2 hours before surgery. **(n=20)** **Pregabalin:** 150mg pregabalin 2 hours before surgery.	Patients undergoing CABG surgery Age - Mean (SD): 61 (7.5) Egypt	• Pain scores • Dose of additional opioids • Adverse events • Length of hospital stay •	Post-extubation pain was controlled with intravenous PCA morphine 2 mg, with a lockout time of 10 min

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=20) **Placebo:** placebo group received identical placebo two hours before induction of anesthesia. In the operating room. **(n=20)**			
Hassani 2015[88]	**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. If the pain score was > 4, analgesia (IV narcotic opiates) was administered. **(n=30)** **Placebo:** 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. If the pain score was > 4, analgesia (IV narcotic opiates) was administered. **(n=30)**	Candidates for Laparoscopic Gastric Bypass surgery, age > 18 years, ASA class II or I, morbid obesity (body mass index [BMI] ≥ 40 kg/m2) Age - Mean (SD): Gabapentin: 33.4 ± 5.7; Placebo: 35.3 ± 9.2 Iran	• Pain scores • Dose of additional opioids • Adverse events	
Hetta 2016[91]	**Pregabalin:** patients received orally 2 hours	Patients ASA I and II, scheduled for unilateral modified radical mastectomy	• Pain scores	Pain scores given as a median value. Intervention groups with different dosages (75mg,150mg

Study	Intervention and comparison	Population	Outcomes	Comments
	before surgery the study medication: pregabalin (75 mg, 150mg, 300mg. 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. **(n=90)** **Placebo:** 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. **(n=30)**	with axillary evacuation Age - Mean (SD): Pregabalin: 47.61 ± 7.27 ; Placebo: 47.4 ± 7.4 Egypt		and 300mg) were combined as there are no pre-defined dosages for perioperative care
Hosseini 2015[93]	**Gabapentin:** Patients given 600mg Gabapentin 2 hours before surgery. 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	Patients ASA I or II scheduled for laparoscopic cholecystectomy Age - Mean (SD): Gabapentin: 40.50 ± 8.38 ; Placebo: 38.14 ± 10.80 Iran	• Pain scores • Dose of additional opioids	

Study	Intervention and comparison	Population	Outcomes	Comments
	lockout Interval of 15 minutes". PCA pump was connected to the patients during the first 24 hours after surgery **(n=22)** **Placebo:** Placebo given 2 hours before surgery. 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. **(n=22)**			
Kerrick 1993[106]	**Amitriptyline**: 50mg of amitriptyline orally in an extemporaneously compounded liquid for for 3 consecutive evenings as a supplement to PCA (opioid) therapy. PCA drug meperidine (3mg/ml) or Morphine sulfate 0.3mg/ml. **(n=14)** **Placebo**: Placebo which was the liquid vehicle without amitriptyline for 72 hours. PCA drug meperidine (3mg/ml) or Morphine sulfate	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 Age - Mean (SD): Amitriptyline: 64.2 ± 11.2 ; Placebo: 59.4 ± 12.0 USA	• Length of stay in hospital	

Study	Intervention and comparison	Population	Outcomes	Comments
	0.3mg/ml. **(n=14)**			
Khademi 2010[107]	**Gabapentin:** Patients enrolled in the gabapentin group received 600 mg (two 300 mg tablets). 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 **(n=45)** **Placebo:** Patients in the placebo group received two placebo (capsules similar in appearance to gabapentin). 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. **(n=45)**	Patients ASA physical status I and II patients of both sexes who were scheduled for elective open cholecystectomy Age - Mean (SD): Gabapentin 51.3±16.7; Placebo: 52.1±13.6 Iran	• Pain score • Dose of additional opioid • Adverse events	
Khan 2011[109]	**Gabapentin:** Gabapentin (600mg, 900mg or 1200mg) capsules were	Patients ASA I presenting for an elective single level lumbar laminectomy under general anaesthesia	• Pain scores • Dose of additional opioid	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. 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. **(n=150)** **Placebo:** 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 expedite its	Age - Mean (SD): Gabapentin: 43.19 ± 10.69; Placebo: 41.0 ± 10.5 Iran		

Study	Intervention and comparison	Population	Outcomes	Comments
	passage into the stomach. 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 **(n=25)**			
Khan 2013[108]	**Gabapentin:** Received oral gabapentin 1200 mg two hours before surgery. 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. **(n=35)** **Placebo**: received oral placebo	Patients undergoing total abdominal hysterectomy Age - Mean (SD): 43.97 ± 4.033 Pakistan	• Pain scores • Dose of additional opioid • Adverse events	Intervention groups with different dosages (600mg, 900mg, 1200mg) were combined as there are no pre-defined dosages for perioperative care

Study	Intervention and comparison	Population	Outcomes	Comments
	capsules two hours before surgery. 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. **(n=35)**			
Khurana 2014[110]	**Gabapentin:** 300mg of Gabapentin 60 minutes preoperatively and 8 hourly for 7 days postoperatively. 1 to 2 mg/kg Tramadol IV when VAS score >3 **(n=30)** **Pregabalin:** 75mg of Pregabalin 60 minutes preoperatively and 8 hourly for 7 days postoperatively. 1 to 2 mg/kg Tramadol IV when VAS score >3 **(n=30)**	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 Age - Mean (SD): Gabapentin: 49 ± 10.4; Pregabalin: 46.9 ± 10.1 India	• Adverse events	
Kim 2017[112]	**Pregabalin:** The pregabalin group received oral pregabalin 150mg orally	Patients ASA class 1 or 2, scheduled to undergo elective wedge resection or	• Pain scores • Dose of additional opioids	

Study	Intervention and comparison	Population	Outcomes	Comments
	1hour before the anesthetic induction. 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 **(n=30)** **Placebo:** The placebo group received placebo drug orally 1hour before the anesthetic induction. 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	lobectomy underVATSwere enrolled in this randomized, placebo-controlled, double-blind trial. Age - Mean (SD): Pregabalin: 56±12; Placebo: 58±9 South Korea	• Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	administered intravenously and repeated if required **(n=30)**			
Leung 2006[127]	**Gabapentin:** Gabapentin 900mg administered 1 to 2 hours before surgery and anesthesia. This dose was continued for the first 3 postoperative days. . PCA IV hydromorphone **(n=9)** **Placebo:** Placebo administered 1 to 2 hours before surgery and anesthesia. This dose was continued for the first 3 postoperative days. PCA IV hydromorphone. **(n=12)**	Patients who were ≥45 years, undergoing surgery involving the spine, requiring general anesthesia and expected to remain in the hospital postoperatively for ≥72 hours Age - Mean (SD): Gabapentin: 57.2 ± 10.3; Placebo: 61.4 ± 11.3 Denmark	• Dose of additional opioid • Pain score	
Marashi 2012[134]	**Gabapentin:** patients received three capsules, each containing 300 mg (a total of 900 mg) gabapentin, two hours before surgery. 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.	Patients ASA I and II whom underwent total thyroidectomy without lymph node dissection (Patients studied were previously diagnosed with multi-nodular goiter) Age - Mean (SD): Gabapentin: 38.5 ± 10.1; Placebo: 38.2 ± 10.0. Iran	• Pain scores • Dose of additional opioid	

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=22) **Placebo:** Placebo capsules given 2 hours before surgery. 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. **(n=22)**			
Mardani-kivi 2013[136]	**Gabapentin:** 600mg of gabapentin 2 hours preoperatively. 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. **(n=57)** **Placebo:** Patients given identical-looking placebo. The placebo was provided in identical form to the original capsule by the same pharmaceutical company 2 hours preoperatively. On-demand pethedine (0.5mg/Kg) was injected for patients' pain management in the first 24 h	Patients aged between 18-55 years, physical condition type I or II in ASA operation duration time less than one hour, and no concurrent lesions identified during arthroscopy. Age - Mean (SD): Gabapentin: 32.2±9.3; Placebo: 30.5±10.2 Iran	• Pain scores • Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	post-operation. No other sedatives or analgesics were given to the patients during the follow-up period. **(n=57)**			
Mardani-Kivi 2016[135]	**Gabapentin:** gabapentin 600 mg two hours prior to the operation. Pethedine (0.5 mg/kg) was injected on demand. None of the patients received other opioids or analgesics peri-operatively. **(n=38)** **Placebo:** 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. Pethedine (0.5 mg/kg) was injected on demand. None of the patients received other opioids or analgesics peri-operatively. **(n=38)**	Patients 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. Age - Mean (SD): Gabapentin: 30.2 ± 5; Placebo: 28.3 ± 4.4 Iran	• Pain scores • Dose of additional opioid • Adverse events	
Metry 2008[144]	**Gabapentin:** two hours prior to induction of anesthesia or two hours after	Patients aged 18-75, scheduled for unilateral modified radical mastectomy with auxillary dissection	• Pain scores • Dose of additional opioids	Intervention groups with different timing but same dosage (pre or post intervention) were combined

Study	Intervention and comparison	Population	Outcomes	Comments
	the end of surgery patients received 1200mg of Gabapentin. All patients received morphine 3mg IV every 10 minutes until VAS scores were 4 or less at rest and 6 or less during mobilization. **(n=74)** **Placebo:** Two hours prior to induction of anesthesia or two hours after the end of surgery patients received Placebo. All patients received morphine 3mg IV every 10 minutes until VAS scores were 4 or less at rest and 6 or less during mobilization. **(n=37)**	Age - Mean (SD): Gabapentin: 57.45 ± 7.806; Placebo: 58.6 ± 8.9 Egypt	• Adverse events	
Mishra 2016[146]	**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. 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. **(n=30)**	Patients ASA I and II of either sex in the age group of 20–60 years, weighing 40–70 kg, scheduled for elective laparoscopic cholecystectomy Age - Mean (SD): Gabapentin: 37 ± 9.37; Pregabalin: 35.8 ± 8.43 India	• Pain scores • Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. 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. **(n=30)**			
Mohammadi 2008[148]	**Gabapentin:** Patients within this group received 400mg Gabapentin 1 hour before surgery. Fentanyl was used as rescue postoperative analgesic and Ondansetron 4mg IV as rescue medication for emesis **(n=35)** **Placebo**: Placebo tablet given 1 hour before surgery. Fentanyl was used as rescue postoperative analgesic and Ondansetron 4mg IV as rescue medication for emesis. **(n=35)**	Patients ASA I or II, aged 20 - 45, scheduled for outpatient laparoscopic surgery under general anaesthesia Age - Mean (SD): Gabapentin: 31.3 ± 5.4; Placebo: 31.9 ± 5.6 Iran	• Pain score • Adverse events	Pain score given as a median value
Mohammed 2012[149]	**Gabapentin:** patients received oral gabapentin 1.2 g 1 h before	Patients ASA I–II, scheduled to undergo elective functional endoscopic sinus surgery. > 18 years old,	• Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	scheduled time for surgery. 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. **(n=40)** **Placebo:** received oral placebo capsules before scheduled time for surgery. 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	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 Age - Mean (SD): Gabapentin: 30.6±6.1; Placebo: 33.7±4.2 Egypt		

Study	Intervention and comparison	Population	Outcomes	Comments
	use. **(n=40)**			
Montazeri 2007[152]	**Gabapentin:** 300 mg capsule of gabapentin was given to the patients about two hours before induction of anaesthesia. Patients received morphine 0.05 mg/kg IV on demand. **(n=35)** **Placebo**: 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. Patients received morphine 0.05 mg/kg IV on demand. **(n=35)**	Patients aged 16-70 years; ASA I -II; duration of surgery between 1.5-2 hours; and scheduled for knee arthroscopy Age - Mean (SD): Gabapentin: 34.7 ± 18.1; Placebo: 34.6 ± 17.8 Iran	• Pain scores • Dose of additional opioid	
Nesioonpour 2014[164]	**Gabapentin:** 800mg oral gabapentin as two 400mg capsules one hour before surgery. IV pethidine 0.3mg/kg was considered to be administered in case of VAS at or above 3. (**n=31)** **Placebo**:	Patients >18 years of age, weighing at least 40kg and ASA I Age - Mean (SD): Gabapentin: 28.43 ± 10.43; Placebo: 28.81 ± 10.44 Iran	• Pain scores • Dose of additional opioid	

Study	Intervention and comparison	Population	Outcomes	Comments
	Two placebo capsules one hour before surgery. IV pethidine 0.3mg/kg was considered to be administered in case of VAS at or above 3. **(n=31)**			
Ozgencil 2011[175]	**Gabapentin:** Patients received gabapentin 600 mg at two hours prior to the operation, and ten and 22 hours after the operation (over two days). 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)** **Pregabalin:** Patients received Pregabalin 150mg at two hours prior to the operation, and ten and 22 hours after the operation (over two days). PCA pump was set to deliver a loading dose of 2.5 mg and an incremental dose of	Patients who were scheduled to undergo elective decompressive lumbar laminectomy and discectomy. Age - Mean (SD): Gabapentin: 50.6 ± 9.1; Pregabalin: 51.9 ± 7.1 Turkey	• Pain scores • Dose of additional opioids • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	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)**			
Pandey 2004[180]	**Gabapentin:** Oral 300 mg gabapentin, two hours before surgery. 2 µg·kg–1 fentanyl was administered intravenously by a staff nurse as a rescue analgesic at the patient's demand **(n=153)** **Tramadol**: 100 mg tramadol or a matching placebo two hours before surgery. 2 µg·kg–1 fentanyl was administered intravenously by a staff nurse as a rescue analgesic at the patient's demand **(n=153)**	Patients ASA I and II of both sexes scheduled for elective laparoscopic cholecystectomy Age - Mean (SD): Gabapentin: 41.65 ± 11.19; Tramadol: 40.03 ± 10.84. India	• Pain scores • Dose of additional opioids • Adverse events	
Pandey 2004[181]	**Gabapentin:** oral gabapentin 300 mg two hours before surgery. Patients received fentanyl 2 (micrograms) µg·kg–1 on	Patients ASA I and II, of both sexes scheduled for single-level lumbar disc surgery Age - Mean (SD): Gabapentin: 38.5 ± 7.7;	• Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	demand. **(n=28)** **Placebo:** matching placebo two hours before surgery. Patients received fentanyl 2 (micrograms) µg·kg–1 on demand. **(n=28)**	Placebo: 39.1 ± 11.6. India		
Pandey 2005[178]	**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). Fentanyl 1.0 µg/kg on each demand with a lockout of 10 minutes **(n=80)** **Placebo:** 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. **(n=20)**	Patients ASA I and II, scheduled for single level lumbar disk surgery Age - Mean (SD): Gabapentin: 41.6± 12.03; Placebo: 36.9±11.5. India	• Pain scores • Dose of additional opioid • Adverse events	Intervention groups with different dosages (300mg, 600mg, 900mg and 1200mg) were combined as there are no pre-defined dosages for perioperative care

Study	Intervention and comparison	Population	Outcomes	Comments
Pandey 2005[182]	**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. Subjects received analgesia via PCA pump (fentanyl 1.0 µg·kg–1 iv on each demand with lockout interval of 5 min). **(n=40)** **Placebo:** Received two capsules of matching placebo two hours before scheduled surgery and two capsules of placebo through a nasogastric tube after surgical incision. Subjects received analgesia via PCA pump (fentanyl 1.0 µg·kg–1 iv on each demand with lockout interval of 5 min). **(n=20)**	ASA I, healthy kidney donors of both sexes and scheduled for open donor nephrectomy Age - Mean (SD): Gabapentin: 44.6 ± 10.47; Placebo: 41.5 ± 12.3 India	• Pain scores • Dose of additional opioid • Adverse events	Intervention groups with different timing but same dosage (pre or post-surgical intervention) were combined
Pandey 2006[179]	**Gabapentin:** Received 600 mg of gabapentin 2 hours before surgery. Patients received patient-controlled-analgesia for their pain management (PCA pump was set to fentanyl 1.0	Patients scheduled for elective laparoscopic cholecystectomy Age - Mean (SD): Gabapentin: 42.8 ± 11.4; Placebo: 41.8 ± 11.1	• Dose of additional opioids • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	mg/kg patient's activated dose with lockout interval of 10 minutes). Patients received ondansetron 4 mg intravenously when they demanded antiemetics. **(n=130)** **Placebo:** Placebo capsules 2 hours before surgery. 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. **(n=130)**	India		
Pandey 2014[177]	**Gabapentin:** Patients received 600 mg of gabapentin (two capsules of 300 mg each) 2 h. before scheduled surgery (n=40) **Pregabalin:** Patients received 150 mg pregabalin (two capsules of 75 mg each) 2 h. before scheduled surgery (n=37)	Patients undergoing laproscopic cholecystectomy Mean age (SD): Gabapentin: 40.5±10.0; Pregabalin: 43.7±10.9 India	• Pain scores • Dose of additional opioid	

Study	Intervention and comparison	Population	Outcomes	Comments
Paulus Lalenoh 2014[121]	**Pregabalin:** 1 hour before surgery pregabalin given 3 mg/kg orally. Both groups postoperative analgesic morphine given iv injection in Patient Controlled Analgesia (PCA) with the help of PCA infuser. **(n=26)** **Placebo:** 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. **(n=26)**	Patients scheduled for hysterectomy Age - Mean (range): Pregabalin: 41.7; Placebo: 40.7 - Range (36-48) Uganda	• Pain scores	Pain scores given as a medial value and post-operative morphine regimen not specified
Radhakrishnan 2005[189]	**Gabapentin:** 400mg of Gabapentin the night before surgery and two hours prior to surgery. 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	Patients 18-65, ASA I or II, undergoing elective lumbar laminectomy and discectomy Age - Mean (SD): Gabapentin: 39.63±10.87; Placebo: 41.67±12.06 India	• Pain scores • Dose of additional opioids • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	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. **(n=30)** **Placebo:** Placebo capsule taken the night before surgery and 2 hours prior to procedure. 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. **(n=30)**			
Routray 2018[196]	**Gabapentin:** Two gabapentin capsules 300mg each with a sip of water 1 hour before the expected time of induction of anesthesia. Rescue analgesia was Tramadol injection of 1.5mg/kg when the VAS score was more than 4 **(n=25)**	Patients 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 anaesthesia	• Dose of additional opioids • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	Pregabalin: Two pregabalin capsules 150mg each with a sip of water 1 hour before the expected time of induction of anesthesia. Rescue analgesia was Tramadol injection of 1.5mg/kg when the VAS score was more than 4. **(n=25)**	Age - Mean (SD): Gabapentin: 35.36 ± 9.97; Pregabalin: 36.56 ± 9.82 India		
Said-Ahmed 2007[203]	**Gabapentin:** 2 hours before surgery patients received Gabapentin (300, 60, or 1200mg). Patients received fentanyl 2 mcg/kg on demand. **(n=60)** **Placebo:** Placebo given orally 2 hours before surgery. Duration preoperatively. Concurrent medication/care: Patients received fentanyl 2 mcg/kg on demand. **(n=20)**	Patients ASA 1 and 2, scheduled for elective myomectomy Age - Mean (SD): Gabapentin: 37.33 ± 6.68; Placebo: 36 ± 7 Egypt	• Pain scores • Dose of additional opioid • Adverse events	Intervention groups with different dosages (300mg, 600mg and 1200mg) were combined as there are no pre-defined dosages for perioperative care
Siddiqui 2014[206]	**Gabapentin:** 600mg of oral Gabapentin 1 hour before surgery. Morphine PCA with a bolus of 1.5mg morphine with a lockout of 5 minutes, and a 4 hour limit of	Patients with an established diagnosis of IBD between 18 - 60 scheduled for open bowel surgery with a midline incision Age - Mean (SD): Gabapentin: 38.1 ± 12.6;	• Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	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 **(n=40)** **Placebo:** Placebo capsules 1 hour before surgery. 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 physician's judgment the pain was not adequately controlled with morphine, they would be switched to hydromorphone PCA in equipotent dose settings. **(n=41)**	Placebo 37.2 ± 13.2 Canada		
Soltanzadeh 2011[210]	**Gabapentin:** 800 mg oral gabapentin two hours before the surgery, followed by 400 mg oral	Patients aged 20-70 years who were candidates for coronary artery bypass graft (CABG) surgery	• Dose of additional opioid	

Study	Intervention and comparison	Population	Outcomes	Comments
	gabapentin two hours after extubation. All patients received intramuscular morphine 10 mg and 25 mg promethazine before transferring to the operating room. Postoperatively, 2 mg morphine was administered intravenously if requested by the patient (NRS≥3) as rescue analgesia. **(n=30)** **Placebo:** Oral placebo two hours before the surgery, followed by placebo two hours after extubation. All patients received intramuscular morphine 10 mg and 25 mg promethazine before transferring to the operating room. Postoperatively, 2 mg morphine was administered intravenously if requested by the patient (NRS≥3) as rescue analgesia. **(n=30)**	Age - Mean (SD): Gabapentin: 58.2±8.3; Placebo: 55.2±8.1 Iran		
Spreng 2011[213]	**Pregabalin:** 150mg Pregabalin one hour before surgery. All patients were pre-medicated with Paracetamol (<60kg - 1000mg; >60kg - 1500mg). Postoperatively patients	Patients scheduled for an elective lumbar single level microdiscectomy Age - Mean (SD): Pregabalin: 44.1 ±10.8; Placebo: 42.9 ± 7.6	• Pain score • Adverse events	Pain scored given as an area under the curve

Study	Intervention and comparison	Population	Outcomes	Comments
	equipped with IV PCA for the first 24 hours, 2mg morphine bolus with a 10 minute lock out time. **(n=25)** **Placebo:** Placebo one hour before surgery. 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. **(n=25)**	Norway		
Srivastava 2010[214]	**Gabapentin:** 600mg of gabapentin orally with sips of water 2h before surgery. 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. **(n=63)** **Placebo**: identical looking capsule placebo orally with sips of water 2h before surgery. All the patients received a bolus dose of 50mg of tramadol followed	Patients ASA I and II patients requiring elective minilap open cholecystectomy Age - Mean (SD): gabapentin: 43±7.06; Placebo: 44.7±9.40 India	• Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	by 20mg on demand with a lockout interval of 15min with a maximum allowable dose of 240mg in 4 h **(n=64)**			
Sundar 2012[220]	**Pregabalin:** **1**50 mg of pregabalin orally 60 min before surgery. 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. **(n=30)** **Placebo:** Placebo capsule similar to pregabalin, 60 minutes before surgery. 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	Patients scheduled for elective Off Pump Coronary Artery Bypass surgery under general anaesthesia Age - Mean (SD): Pregabalin: 60.1 ± 8.6; Placebo: 57.2 ± 7.6 India	• Pain scores • Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	mg/day, aspirin 75 mg/day, to inhibit platelet aggregation, and 20 mg/day pantoprazole for gastric protection. **(n=30)**			
Syal 2010[223]	**Gabapentin:** Patients received 1200 mg of Gabapentin packed in 5 capsules 2 hours before induction. 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. **(n=30)** **Placebo**: Patients received 5 placebo capsules filled with thin sugar 2 hours before induction. 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. **(n=30)**	Patients ASA I and II, 20 to 50 years, weighing between 40 to 65 kg and undergoing elective surgery (open cholecystectomy) under general anesthesia. Age - Mean (SD): Gabapentin: 39.97 ± 6.20; Placebo: 39.60 ± 7.69 India	• Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
Tuncer 2005[232]	**Gabapentin:** Received Gabapentin (1200mg or 800mg) 1 hour before surgery. PCA morphine set to deliver morphine 1mg in a 1ml solution on demand. The lockout interval was set to 7 minutes. **(n=30)** **Placebo:** Placebo capsule given 1 hour before surgery. PCA morphine set to deliver morphine 1mg in a 1ml solution on demand. The lockout interval was set to 7 minutes **(n=15)**	Patients ASA I or II scheduled to undergo major orthopaedic surgery with general anaesthesia Age - Mean (SD): Gabapentin: 37.05 ± 16.04; Placebo: 37.8 ± 16.6 Turkey	• Pain scores • Dose of additional opioid • Adverse events	Intervention groups with different dosages (800mg and 1200mg) were combined as there are no pre-defined dosages for perioperative care
Turan 2004[233]	**Gabapentin:** 1,200 mg gabapentin 1 hour before surgery. 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)** **Placebo:** Oral placebo 1 hour before	Patients undergoing elective lumbar discectomy or spinal fusion surgery ≥18 yr old, weighed more than 40 kg, and could operate a patient-controlled analgesia (PCA) device Age - Mean (SD): Gabapentin: 48 ± 9; Placebo: 45 ± 8. Turkey	• Pain scores • Dose of additional opioid • Adverse events	Pain scores given as a median value

Study	Intervention and comparison	Population	Outcomes	Comments
	surgery. 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)**			
Turan 2004[234]	**Gabapentin:** 1200 mg gabapentin 1 hour before surgery. 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. **(n=25)** **Placebo:** Oral placebo capsules 1 hour before surgery . 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	Patients aged 18 yr old, weighed more than 40 kg, and could operate a PCA device, undergoing total abdominal hysterectomy with salpingo-oophorectomy Age - Mean (SD): Gabapentin: 52.5 ± 11.2; Placebo: 50.4 ± 10.2 Turkey	• Pain scores • Dose of additional opioid • Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	1 h. **(n=25)**			
Vahedi 2011[240]	**Gabapentin:** 300mg Gabapentin 2 hours before surgery. 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. **(n=103)** **Placebo:** Identical placebo taken 2 hours before surgery. 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. **(n=103)**	Patients >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. Age - Mean (SD): Gabapentin: 44.5 ± 10.374; Placebo: 44.4 ± 10.558 Iran	• Pain scores • Dose of additional opioid	Secondary exclusion criteria applied to the participants after surgical intervention was completed
Waikakul 2011[241]	**Gabapentin:** Gabapentin 400 mg one to two hours before anesthesia and then gabapentin 300 mg 12	Patients aged18-80 years, ASA I, II, or III undergoing major spinal surgery (decompression or fixation or reconstruction)	• Pain scores • Dose of additional opioid • Adverse events	Pain scores and dose of additional morphine consumption gives as median values

Study	Intervention and comparison	Population	Outcomes	Comments
	and 24 hours later. 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 in 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	Age - Mean (SD): Gabapentin: 44.7 ± 19.4; Placebo: 50.4 ± 13.6 Thailand		

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=28) **Placebo:** Placebo one to two hours before anesthesia and placebo 12 and 24 hours later. 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 in 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			

Study	Intervention and comparison	Population	Outcomes	Comments
	every 15 minute until the pain was relieved. The loading dose of morphine was recorded. The patient was connected to a PCA pump **(n=28)**			
White 2009[249]	**Pregabalin:** 60–90 min before induction of general anesthesia participants were given Pregabalin (75mg, 150mg, or 300mg) orally. 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. **(n=81)** **Placebo:** Oral placebo 60–90 min before induction of general anesthesia. 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.. **(n=27)**	Patients ASA I–III patients, aged 18–70 yr, scheduled for elective ambulatory and short-stay (<24 h) surgical procedures e.g., ear–nose–throat, laparoscopic, urologic and plastic surgery Age - Mean (SD): Pregabalin: 45.67 ± 14.53; Placebo: 48 ± 15 USA	• Pain scores • Dose of additional opioid • Adverse events	Intervention groups with different dosages (75mg, 150mg and 300mg) were combined as there are no pre-defined dosages for perioperative care

Study	Intervention and comparison	Population	Outcomes	Comments
Yucel 2011[256]	**Pregabalin:** Receive pregabalin (150mg or 300mg) 4 hours before the induction of anesthesia and at 12 hours postoperatively. 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. **(n=60)** **Placebo**: Receive Placebo 4 hours before the induction of anesthesia and at 12 hours postoperatively. 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	Patients ASA I or II; 25 - 65 years of age scheduled for elective total abdominal hysterectomy under general anesthesia. Age - Mean (SD): Pregabalin: 44.84 ± 8.44; Placebo: 42.47 ± 9.31 Turkey	• Pain scores • Dose of additional opioid • Adverse events	Intervention groups with different dosages (150mg and 300mg) were combined as there are no pre-defined dosages for perioperative care

Study	Intervention and comparison	Population	Outcomes	Comments
	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. **(n=30)**			
Ziyaeifard 2015[259]	**Pregabalin:** 150mg Pregabalin given 2 hours before surgery. Patients having VAS scores > 3 received 0.1 mg/kg of intravenous morphine up to 8 mg. **(n=30)** **Placebo**: Placebo given 2 hours before surgery. Patients having VAS scores > 3 received 0.1 mg/kg of intravenous morphine up to 8 mg. **(n=30)**	Patients scheduled for coronary artery bypass graft > 20 years of age and ASA I - III Age - Mean (SD): Pregabalin: 54.7 ± 8.3; Placebo: 57.9 ± 8.6 Iran	• Dose of additional opioid	

See appendices for full evidence tables.

5.3.4 Quality assessment of clinical studies included in the evidence review

Table 58: Clinical evidence summary: Gabapentin compared to Placebo for managing acute post-operative pain

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Gabapentin (95% CI)
Pain score ≤6 hours Scale from: 0 to 10.	1706 (23 studies) 6 hours	⊕⊖⊖⊖ VERY LOW1,2 due to inconsistency, imprecision		The mean pain score ≤6 hours in the control groups was 5.03	The mean pain score ≤6 hours in the intervention groups was 1.46 lower (1.91 to 1.01 lower)
Pain score 24 hours Scale from: 0 to 10.	1579 (21 studies) 24 hours	⊕⊕⊖⊖ LOW1,2 due to inconsistency		The mean pain score 24 hours in the control groups was 3.212	The mean pain score 24 hours in the intervention groups was 0.87 lower (1.29 to 0.46 lower)
Dose of opioid consumed ≤6h	560 (9 studies) 6 hours	⊕⊕⊖⊖ LOW1,2 due to inconsistency, imprecision			The mean dose of opioid consumed ≤6h in the intervention groups was 0.77 standard deviations lower (1.12 to 0.42 lower)
Dose of opioid consumed 24h	2439 (30 studies) 24 hours	⊕⊕⊖⊖ LOW1,2 due to inconsistency			The mean dose of opioid consumed 24h in the intervention groups was 1.80 standard deviations lower (2.2 to 1.4 lower)
Respiratory Depression	220 (2 studies)	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.06 (0.21 to 5.27)	Moderate	
				33 per 1000	2 more per 1000 (from 26 fewer to 141 more)
Nausea ≤6 hours	171 (3 studies) 6 hours	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.1 (0.78 to 1.56)	Moderate	
				400 per 1000	40 more per 1000 (from 88 fewer to 224 more)
Nausea 24 hours	1479 (20 studies) 24 hours	⊕⊕⊕⊖ MODERATE2 due to imprecision	RR 0.77 (0.63 to 0.95)	Moderate	
				250 per 1000	58 fewer per 1000 (from 13 fewer to 93 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Gabapentin (95% CI)
Vomiting ≤6 hours	105 (2 studies) 6 hours	⨁⨁⨀⨀ LOW2 due to imprecision	RR 0.97 (0.67 to 1.4)	Moderate	
				400 per 1000	12 fewer per 1000 (from 132 fewer to 160 more)
Vomiting 24 hours	1579 (21 studies) 24 hours	⨁⨁⨁⨀ MODERATE2 due to imprecision	RR 0.66 (0.51 to 0.83)	Moderate	
				167 per 1000	57 fewer per 1000 (from 28 fewer to 82 fewer)
Nausea & Vomiting ≤ 6 hours	179 (2 studies) 6 hours	⨁⨁⨁⨀ MODERATE1 due to inconsistency	RR 0.32 (0.13 to 0.76)	Moderate	
				228 per 1000	155 fewer per 1000 (from 55 fewer to 198 fewer)
Nausea & Vomiting	756 (7 studies) Postoperative	⨁⨁⨀⨀ LOW1,2 due to inconsistency, imprecision	RR 0.67 (0.42 to 1.07)	Moderate	
				467 per 1000	154 fewer per 1000 (from 271 fewer to 33 more)
Dizziness ≤6 hours	350 (5 studies) 6 hours	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1.04 (0.69 to 1.56)	Moderate	
				235 per 1000	9 more per 1000 (from 73 fewer to 132 more)
Dizziness 24 hours	1126 (15 studies) 24 hours	⨁⨁⨁⨀ MODERATE2 due to imprecision	RR 1.29 (0.95 to 1.77)	Moderate	
				74 per 1000	21 more per 1000 (from 4 fewer to 57 more)
Somnolance ≤ 6 hours	65 (1 study) 6 hours	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1 (0.7 to 1.43)	Moderate	
				647 per 1000	0 fewer per 1000 (from 194 fewer to 278 more)
Somnolance 24 hours	1011 (12 studies) 24 hours	⨁⨁⨁⨀ MODERATE2 due to imprecision	RR 1.72 (0.93 to 3.18)	Moderate	
				40 per 1000	29 more per 1000 (from 3 fewer to 87 more)
Sedation ≤6 hours	179 (2 studies)	⨁⨁⨀⨀ LOW2	RR 1.48 (0.6 to	Moderate	
				87 per 1000	42 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Gabapentin (95% CI)
	6 hours	due to imprecision	3.63)		(from 35 fewer to 229 more)
Sedation	419 (5 studies) Postoperative	⊕⊕⊕⊖ MODERATE2 due to imprecision	RR 1.16 (0.92 to 1.47)	Moderate	
				133 per 1000	21 more per 1000 (from 11 fewer to 63 more)
Urinary Retention	434 (7 studies) Postoperative	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.78 (0.42 to 1.47)	Moderate	
				28 per 1000	6 fewer per 1000 (from 16 fewer to 13 more)
Dry Mouth	132 (2 studies) Postoperative	⊕⊕⊖⊖ LOW2 due to imprecision	Peto OR 7.39 (0.15 to 372.38)	Moderate	
				500 per 1000	381 more per 1000 (from 370 fewer to 497 more)
Pruritus	828 (10 studies) Postoperative	⊕⊕⊕⊖ MODERATE2 due to imprecision	Peto OR 0.62 (0.35 to 1.09)	Moderate	
				80 per 1000	29 fewer per 1000 (from 50 fewer to 7 more)
Headache ≤ 6 hours	110 (2 studies) 6 hours	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.91 (0.34 to 2.45)	Moderate	
				148 per 1000	13 fewer per 1000 (from 98 fewer to 215 more)
Headache	552 (6 studies) Postoperative	⊕⊕⊖⊖ LOW2 due to imprecision	Peto OR 0.67 (0.29 to 1.56)	Moderate	
				70 per 1000	22 fewer per 1000 (from 49 fewer to 35 more)
Light headed	353 (5 studies) Postoperative	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.04 (0.77 to 1.39)	Moderate	
				100 per 1000	4 more per 1000 (from 23 fewer to 39 more)
Length of stay	38 (1 study)	⊕⊕⊕⊖ MODERATE2 due to imprecision		The mean length of stay in the control groups was 7.6 days	The mean length of stay in the intervention groups was 0.80 lower (2.32 lower to 0.72 higher)

1 Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Gabapentin (95% CI)
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 59: Clinical evidence summary: Pregabalin compared to Placebo for managing acute post-operative pain

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pregabalin (95% CI)
Pain score ≤6 hours Scale from: 0 to 10.	435 (6 studies) 6 Hours	⊕⊖⊖⊖ VERY LOW1,2 due to inconsistency, imprecision		The mean pain score ≤6 hours in the control groups was 3.81	The mean pain score ≤6 hours in the intervention groups was 0.89 lower (1.55 to 0.24 lower)
Pain score 24 hours Scale from: 0 to 10.	435 (6 studies) 24 hours	⊕⊕⊖⊖ LOW1 due to inconsistency		The mean pain score 24 hours in the control groups was 2.039	The mean pain score 24 hours in the intervention groups was 0.18 lower (0.61 lower to 0.25 higher)
Dose of opioid consumed ≤6h	520 (7 studies) 6 hours	⊕⊕⊖⊖ LOW1,2 due to inconsistency, imprecision			The mean dose of opioid consumed ≤6h in the intervention groups was 0.91 standard deviations lower (1.75 to 0.07 lower)
Dose of opioid consumed 24h	419 (7 studies) 24 hours	⊕⊕⊖⊖ LOW1,2 due to inconsistency			The mean dose of opioid consumed 24h in the intervention groups was 1.47 standard deviations lower (2.26 to 0.69 lower)
Nausea ≤ 6 hours	60 (1 study)	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1 (0.4 to 2.5)	Moderate	
				233 per 1000	0 fewer per 1000 (from 140 fewer to 350 more)
Nausea 24 hours	425	⊕⊕⊕⊖	RR 0.62	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pregabalin (95% CI)
	(7 studies) 24 hours	MODERATE2 due to imprecision	(0.43 to 0.88)	200 per 1000	76 fewer per 1000 (from 24 fewer to 114 fewer)
Vomiting 24 hours	425 (7 studies) 24 hours	⊕⊕⊕⊕ HIGH2	RR 0.52 (0.34 to 0.78)	Moderate	
				83 per 1000	40 fewer per 1000 (from 18 fewer to 55 fewer)
Nausea & Vomiting	176 (2 studies) Postoperatively	⊕⊕⊖⊖ LOW1 due to imprecision	RR 1 (0.63 to 1.6)	Moderate	
				317 per 1000	0 fewer per 1000 (from 117 fewer to 190 more)
Sedation ≤ 6 hours	60 (1 study) 6 hours	⊕⊕⊖⊖ LOW2 due to imprecision	Peto Odds 7.39 (0.15 to 372.38)	Moderate	
				0 per 1000	Not estimable
Sedation 24 hours	106 (2 studies) 24 hours	⊕⊕⊖⊖ LOW2 due to imprecision	Peto Odds 1.71 (0.27 to 10.74)	Moderate	
				42 per 1000	30 more per 1000 (from 31 fewer to 409 more)
Ramsay Sedation Score ≤ 6 hours Scale from: 0 to 6.	180 (2 studies) 6 hours	⊕⊕⊕⊖ MODERATE2 due to imprecision		The mean ramsay sedation score ≤ 6 hours in the control groups was 1.64	The mean ramsay sedation score ≤ 6 hours in the intervention groups was 0.32 higher (0.1 to 0.54 higher)
Ramsay Sedation Score 24hours Scale from: 0 to 6.	90 (1 study) 24 hours	⊕⊕⊕⊖ MODERATE2 due to imprecision		The mean ramsay sedation score 24hours in the control groups was 1.1	The mean ramsay sedation score 24hours in the intervention groups was 0.07 higher (0.08 lower to 0.22 higher)
Dizziness ≤ 6 hours	168 (2 studies) 6 hours	⊕⊕⊕⊖ MODERATE2 due to imprecision	RR 3 (0.8 to 11.2)	Moderate	
				52 per 1000	104 more per 1000 (from 10 fewer to 530 more)
Dizziness 24 hours	293 (5 studies)	⊕⊕⊖⊖ LOW2	RR 1.15 (0.66 to 2)	Moderate	
				154 per 1000	23 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pregabalin (95% CI)
	24 hours	due to imprecision			(from 52 fewer to 154 more)
Pruritus	266 (4 studies) Postoperatively	⨁⨁⨁⊖ MODERATE2 due to imprecision	RR 0.51 (0.26 to 1.04)	Moderate	
				150 per 1000	74 fewer per 1000 (from 111 fewer to 6 more)
Urinary Retention	136 (2 studies) Postoperatively	⨁⨁⊖⊖ LOW2 due to imprecision	RR 0.82 (0.31 to 2.2)	Moderate	
				121 per 1000	22 fewer per 1000 (from 83 fewer to 145 more)
Respiratory Depression	102 (2 studies) Postoperatively	⨁⨁⊖⊖ LOW2 due to imprecision	RR 4.32 (0.5 to 37.31)	Moderate	
				0 per 1000	-
Headache ≤ 6 hours	60 (1 study) 6 hours	⨁⨁⊖⊖ LOW2 due to imprecision	RR 1.25 (0.37 to 4.21)	Moderate	
				133 per 1000	33 more per 1000 (from 84 fewer to 427 more)
Headache 24 hours	162 (3 studies) 24 hours	⨁⨁⊖⊖ LOW2 due to imprecision	RR 1.14 (0.56 to 2.32)	Moderate	
				133 per 1000	19 more per 1000 (from 59 fewer to 176 more)
Somnolence	127 (2 studies) Postoperatively	⨁⨁⊖⊖ LOW2 due to imprecision	RR 2.0 (0.48 to 8.35)	Moderate	
				33 per 1000	33 more per 1000 (from 17 fewer to 243 more)
Length of stay	37 (1 study)	⨁⨁⊖⊖ LOW2 due to imprecision		The mean length of stay in the control groups was 7.6	The mean length of stay in the intervention groups was 0.30 lower (2.24 lower to 1.64 higher)

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 60: Clinical evidence summary: Gabapentin compared to Pregabalin for managing acute post-operative pain

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Pregabalin	Risk difference with Gabapentin (95% CI)
Pain score ≤6 hours Scale from: 0 to 10.	157 (3 studies) 6 hours	⊕⊖⊖⊖ VERY LOW1,2 due to inconsistency, imprecision		The mean pain score ≤6 hours in the control groups was 2.862	The mean pain score ≤6 hours in the intervention groups was 0.47 lower (1.55 lower to 0.62 higher)
Pain score 24 hours Scale from: 0 to 10.	178 (4 studies) 24 hours	⊕⊕⊕⊕ HIGH		The mean pain score 24 hours in the control groups was 1.983	The mean pain score 24 hours in the intervention groups was 0.05 higher (0.09 lower to 0.18 higher)
Dose of Opioid <6 hours	72 (1 study)	⊕⊕⊕⊖ MODERATE3 due to risk of bias			The mean dose of opioid <6 hours in the intervention groups was 2.80 lower (3.99 to 1.61 lower)
Dose of opioid consumed 24h	372 (7 studies) 24 hours	⊕⊖⊖⊖ VERY LOW1,2 due to inconsistency, imprecision			The mean dose of opioid consumed 24h in the intervention groups was 0.59 standard deviations higher (1.08 lower to 2.25 higher)
Sedation	170 (3 studies) Postoepratively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.95 (0.58 to 1.56)	Moderate	
				200 per 1000	10 fewer per 1000 (from 84 fewer to 112 more)
Respiratory Depression	60 (1 study) Postoperatively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.67 (0.12 to 3.71)	Moderate	
				100 per 1000	33 fewer per 1000 (from 88 fewer to 271 more)
Nausea	279 (5 studies) Postoperatively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.03 (0.63 to 1.68)	Moderate	
				133 per 1000	4 more per 1000 (from 49 fewer to 90 more)
Vomiting	279 (5 studies) Postoperatively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.22 (0.76 to 1.95)	Moderate	
				100 per 1000	22 more per 1000 (from 24 fewer to 95 more)
Nausea & Vomiting	60	⊕⊕⊖⊖	RR 1.25	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Pregabalin	Risk difference with Gabapentin (95% CI)
	(1 study) Postoperatively	LOW2 due to imprecision	(0.37 to 4.21)	133 per 1000	33 more per 1000 (from 84 fewer to 427 more)
Dizziness	147 (3 studies) Postoperatively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.19 (0.65 to 2.16)	Moderate	
				213 per 1000	40 more per 1000 (from 75 fewer to 247 more)
Somnolance	97 (2 studies) Postoperatively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.07 (0.52 to 2.19)	Moderate	
				233 per 1000	16 more per 1000 (from 112 fewer to 277 more)
Urine Retention	60 (1 study) Postoperatively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.8 (0.24 to 2.69)	Moderate	
				167 per 1000	33 fewer per 1000 (from 127 fewer to 282 more)
Headache	60 (1 study) Postoperatively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 2.5 (0.53 to 11.89)	Moderate	
				67 per 1000	101 more per 1000 (from 31 fewer to 730 more)
Pruritus	60 (1 study) Postoperatively	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.25 (0.37 to 4.21)	Moderate	
				133 per 1000	33 more per 1000 (from 84 fewer to 427 more)
Length of stay	37 (1 study)	⊕⊕⊕⊖ MODERATE2 due to imprecision		The mean length of stay in the control groups was 7.3 days	The mean length of stay in the intervention groups was 0.50 lower (2.21 lower to 1.21 higher)

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 61: Clinical evidence summary: Gabapentin compared to Opioid for managing acute post-operative pain

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Gabapentin (95% CI)
Pain score ≤6 hours Scale from: 0 to 10.	306 (1 study) 6 hours	⨁⨁⊖⊖ LOW1,2 due to indirectness, imprecision		The mean pain score ≤6 hours in the control groups was 2.97	The mean pain score ≤6 hours in the intervention groups was 0.32 lower (0.92 lower to 0.28 higher)
Pain score 24 hours Scale from: 0 to 10.	306 (1 study) 24 hours	⨁⨁⊖⊖ LOW1,2 due to indirectness, imprecision		The mean pain score 24 hours in the control groups was 0.87	The mean pain score 24 hours in the intervention groups was 0.22 lower (0.71 lower to 0.27 higher)
Dose of opioid consumed 24h	306 (1 study) 24 hours	⨁⨁⨁⊖ MODERATE1 due to indirectness		The mean dose of opioid consumed 24h in the control groups was 269.6	The mean dose of opioid consumed 24h in the intervention groups was 48.44 lower (59.3 to 37.58 lower)
Sedation	306 (1 study) Postoperative	⨁⨁⊖⊖ LOW1,2 due to indirectness, imprecision	RR 1.18 (0.85 to 1.65)	Moderate	
				288 per 1000	52 more per 1000 (from 43 fewer to 187 more)
Nausea & Vomiting	306 (1 study) Postoperative	⨁⨁⊖⊖ LOW1,2 due to indirectness, imprecision	RR 1.46 (0.94 to 2.28)	Moderate	
				170 per 1000	78 more per 1000 (from 10 fewer to 218 more)
Respiratory Depression	306 (1 study) Postoperative	⨁⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision	RR 0.08 (0 to 1.35)	Moderate	
				39 per 1000	36 fewer per 1000 (from 39 fewer to 14 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioid	Risk difference with Gabapentin (95% CI)
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 62: Clinical evidence summary: Amitriptyline compared to Placebo for managing acute post-operative pain

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Amitriptyline (95% CI)
Length of hospital stay	24 (1 study) Postoperative	⨁⨁⊖⊖ LOW1 due to imprecision		The mean length of hospital stay in the control groups was 7.9 days	The mean length of hospital stay in the intervention groups was 1.5 days higher (1.03 lower to 4.03 higher)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 63: Evidence not suitable for GRADE analysis: Gabapentin compared to Placebo for managing acute post-operative pain

Outcome	Study (no. of participants)	Risk of bias	Comparison results (Placebo)	Intervention results (Gabapentin)	*P* value
Pain score ≤ 6 hours Scale from: 0 to 10.	Clarke 2013 [41] (n=50)	High	Median (Interquartile range) 0(0-2)	Median (Interquartile range) 0(0-1)	n/a

Outcome	Study (no. of participants)	Risk of bias	Comparison results (Placebo)	Intervention results (Gabapentin)	*P* value
	Dirks 2002[57] (n=70)	High	Median (Interquartile range) 12 (9–30)	Median (Interquartile range) 7 (1–18)	n/a
	Mohammadi 2008 [148] (n=70)	High	Median (Interquartile range) 3 (3 - 5)	Median (Interquartile range) 3 (2 - 3)	n/a
	Radhakrishnan 2005 [189] (n=60)	Low	Median (range) 2 (0-7)	Median (range) 2 (0-6)	n/a
	Turan 2004[233] (n=50)	Low	Median (Interquartile range) 2 (0–4)	Median (Interquartile range) 0(0–2)	n/a
	Waikakul 2011 [241] (n=99)	High	Median (Interquartile range) 6.0 (0-10)	Median (Interquartile range) 5.0 (0-10)	n/a
Pain score >6 - 24 hours Scale from: 0 to 10.	Radhakrishnan 2005 [189] (n=60)	Low	Median (range) 1 (0-5)	Median (range) 1 (0-4)	n/a
	Turan 2004[233] (n=50)	Low	Median (Interquartile range) 0 (0–3)	Median (Interquartile range) 0 (0–2)	n/a
	Waikakul 2011 [241] (n=99)	High	Median (Interquartile range) 3.5 (0-7)	Median (Interquartile range) 3.0 (0-8)	n/a
McGill Pain score Scale from: 0 – 220 (SF-MPQ-2)	Clarke 2013 [41] (n=50)	High	Median (Interquartile range) 0.5 (0.1-1.2)	Median (Interquartile range) 0.6 (0.1-1.2)	n/a

Outcome	Study (no. of participants)	Risk of bias	Comparison results (Placebo)	Intervention results (Gabapentin)	*P* value
Dose of Opioid Consumption ≤ 6 hours	Dirks 2002[57] (n=70)	High	Median (Interquartile range) 29 (21–23) Milligrams	Median (Interquartile range) 15 (10–19) Milligrams	n/a
	Waikakul 2011 [241] (n=99)	High	Median (Interquartile range) 5.0 (0-14) Milligrams	Median (Interquartile range) 4.5 (0-11) Milligrams	n/a
Dose of Opioid Consumption >6 - 24 hours	Waikakul 2011 [241] (n=99)	High	Median (Interquartile range) 18 (1-63) Milligrams	Median (Interquartile range) 15.5 (0-37) Milligrams	n/a
Sedation score Scale from: -5 to +4 (Richmond Agitation Sedation Scale)	Clarke 2013 [41] (n=50)	High	Median (Interquartile range) 5(2-8)	Median (Interquartile range) 7(5-8)	n/a
Anxiety Score (NRS) Scale from: 0 to 10`.	Clarke 2013 [41] (n=50)	High	Median (Interquartile range) 4.0 (2.0- 5.0)	Median (Interquartile range) 2.5 (1.0-4.0)	n/a
Somnolence ≤ 6 hours	Dierking 2004 [55] (n=80)	High	Median (Interquartile range) 0.5 (0-1)	Median (Interquartile range) 1 (0-1.5)	n/a
Somnolence 24 hours	Dierking 2004 [55] (n=80)	High	Median (Interquartile range) 0 (0-0)	Median (Interquartile range) 0 (0-0)	n/a
Somnolence	Siddiqui 2014 [206] (n=82)	Low	Number of events: 38/36	Number of events: 28/36	0.22

Table 64: Evidence not suitable for GRADE analysis: Pregabalin compared to Placebo for managing acute post-operative pain

Outcome	Study (no. of participants)	Risk of bias	Comparison results (Placebo)	Intervention results (Pregabalin)	*P* value
Pain score ≤ 6 hours Scale from: 0 to 10.	Agarwal 2008 [4] (n=60)	High	Median (Range) 4.0 (3.8)	Median (Range) 3.0 (2.0)	n/a
	Hetta 2016 [91] (n=120)	Low	Median (Interquartile range) 2 (1-2)	Median (Interquartile range) (75mg) 2 (1-2); (150mg) 1 (1-2); (300mg) 1 (0-2)	n/a
	Paulus 2014 [121] (n=52)	High	Median (Range) 55 (40-75)	Median (Range) 40 (30-50)	n/a
Pain at rest (VAS 0 – 10) 30-240 minutes	Spreng 2011 [213] (n=50)	High	Area Under Curve 4930 ± 2279	Area Under Curve 3227 ± 2037	n/a
Pain score >6 - 24 hours Scale from: 0 to 10.	Agarwal 2008 [4] (n=60)	High	Median (Range) 3.5 (4.0)	Median (Range) 2.0 (2.0)	n/a
	Hetta 2016 [91] (n=120)	Low	Median (Interquartile range) 2 (1-2)	Median (Interquartile range) (75mg) 1.5 (1-2); (150mg) 1 (1-2); (300mg) 1 (0-2)	n/a
	Paulus 2014 [121] (n=52)	High	Median (Range) 30 (20-40)	Median (Range) 20 (20-40)	n/a
Dose of Opioid Consumption >6 - 24 hours	Agarwal 2008 [4] (n=60)	High	Median (Interquartile Range) 757.5 (99.3) Micrograms	Median (Interquartile Range) 555.2 (124.8) Micrograms	n/a

Outcome	Study (no. of participants)	Risk of bias	Comparison results (Placebo)	Intervention results (Pregabalin)	*P* value
	Paulus 2014 [121] (n=52)	High	Median (Range) 10 (6-15) Milligrams	Median (Range) 7 (5-10) Milligrams	n/a
Sedation Score Scale from: 1 to 6 (Ramsay Sedation Scale)	Agarwal 2008 [4] (n=60)	High	Median (Range) 2 (1)	Median (Range) 3 (1)	n/a

Table 65: Evidence not suitable for GRADE analysis: Gabapentin compared to Pregabalin for managing acute post-operative pain

Outcome	Study (no. of participants)	Risk of bias	Comparison results	Intervention results	*P* value
Pain score ≤ 6 hours Scale from: 0 to 100.	Pandey 2014 [177] (n=115)	High	Mean: Pregabalin: 45.24	Mean: Gabapentin: 56.15	n/a
Pain score 6 - 24 hours Scale from: 0 to 100.	Pandey 2014 [177] (n=115)	High	Mean: Pregabalin: 56.37	Mean: Gabapentin: 60.44	n/a

See appendices for full GRADE tables.

5.4 Economic evidence

5.4.1 Included studies

No health economic studies were included.

5.4.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendices.

5.4.3 Unit costs

The average daily costs of neuropathic nerve stabilisers are provided in Table 66 to help aid consideration of cost effectiveness. A breakdown of these costs is provided in the appendices for the pain evidence review.

Table 66: Average daily costs of neuropathic nerve stabilisers

Analgesic	Average daily cost per person
Amitriptylin	£0.03
Gabapentin	£0.05
Nortriptylline	£0.17
Pregabalin	£0.12

Sources: British National Formulary, Accessed September 2019[101]; Electronic market information tool (eMIT), Accessed September 2019[43]

5.5 Evidence statements

5.5.1 Clinical evidence statements

No outcomes were reported for health related quality of life or the following important outcomes; psychological distress and mental well-being, symptom scores, functional measures and hospital readmission.

Gabapentin vs Placebo

Pain

Twenty three studies found a clinically important benefit with Gabapentin when assessing pain score up to six hours postoperatively compared to placebo (23 studies, n=1706, very low quality evidence)

Twenty one studies found no clinically important difference in pain scores between Gabapentin and placebo from six hours to twenty four hours postoperatively (21 studies, n=1579, very low quality evidence)

Rescue medication

Nine studies showed a clinically important benefit with Gabapentin for the dose of opioid used within 6 hours postoperatively compared to placebo (9 studies, n=560, low quality evidence)

Thirty studies found a clinically important benefit with Gabapentin in the dose of opioid consumed up to twenty four hours postoperatively compared to placebo (30 studies, n=2439, low quality evidence)

Adverse events

Two studies found no clinically important difference between Gabapentin and placebo in rates of respiratory depression (2 studies, n=220, low quality evidence)

Three studies found no clinically important difference between Gabapentin and placebo in rates of nausea under six hours postoperatively (3 studies, n=171, low quality evidence)

Twenty studies found no clinically importance difference between Gabapentin and placebo in rates of nausea up to twenty four hours postoperatively (20 studies, n=1479, moderate quality evidence)

Two studies found no clinically important difference in vomiting under six hours postoperatively between Gabapentin and placebo (2 studies, n=105, low quality evidence)

Twenty one studies found no clinically important difference between Gabapentin and placebo in vomiting rates twenty four hours postoperatively (21 studies, n=1579, moderate quality evidence)

Two studies showed a clinically important benefit with Gabapentin for rates of nausea and vomiting six hours postoperatively compared to placebo (2 studies, n=179, moderate quality evidence)

Seven studies found a clinically important benefit with Gabapentin in overall rates of nausea and vomiting compared to placebo (7 studies, n=756, low quality evidence)

Five studies showed no clinically important difference between Gabapentin and placebo for dizziness under six hours postoperatively (5 studies, n=350, low quality evidence)

Fifteen studies showed no clinically important difference between Gabapentin and placebo in rates of dizziness from six to twenty four hours postoperatively (15 studies, n=1126, moderate quality evidence)

One study found no clinically important difference between Gabapentin and placebo in the rates of somnolence under six hours postoperatively (1 study, n=65, low quality evidence)

Twelve studies showed no clinically important difference between Gabapentin and placebo for in the rates of somnolence at 24 hours postoperatively (12 studies, n=1011, low quality evidence)

Two studies found no difference between Gabapentin and placebo in sedation rates under six hours postoperatively (2 studies, n=179, moderate quality evidence)

Five studies showed no clinically important difference between Gabapentin and placebo in rates of sedation overall (5 studies, n=419, moderate quality evidence)

Seven studies showed no clinically important difference between Gabapentin and placebo for postoperative urinary retention (7 studies, n=434, low quality evidence)

Two studies found a clinically important harm with Gabapentin for postoperative dry mouth compared to placebo (2 studies, n=132, low quality evidence)

Ten studies found no clinically important difference between Gabapentin and placebo in postoperative pruritus (10 studies, n=828, moderate quality evidence)

Two studies showed no clinically important difference between Gabapentin and placebo in rates of headache under six hours (2 studies, n=110, low quality evidence)

Six studies found no clinically important difference between Gabapentin and placebo in postoperative headache (6 studies, n=552, low quality evidence)

Five studies showed no clinically important difference between Gabapentin and placebo in postoperative light-headedness (5 studies, n=353, low quality evidence)

Length of stay

One study found a clinically important benefit for length of stay with gabapentin compared to placebo (1 study, n=38, moderate quality evidence)

Pregabalin vs Placebo

Pain

Six studies showed a clinically important benefit with Pregabalin when assessing pain score up to six hours postoperatively compared to placebo (6 studies, n=435, very low quality evidence)

Six studies found no clinically important difference in pain scores between Pregabalin and palcebo twenty four hours postoperatively (6 studies, n=435, low quality evidence)

Rescue medication

Seven studies showed a clinically important benefit with pregabalin when assessing the dose of opioid used within 6 hours postoperatively compared to placebo (7 studies, n=520, low quality evidence)

Seven studies found a clinically important benefit with pregabalin in the dose of opioid consumed up to twenty four hours postoperatively compared to placebo (7 studies, n=419, low quality evidence)

Adverse events

One study found no clinically important difference between Pregabalin and placebo in rates of nausea under six hours postoperatively (1 study, n=60, low quality evidence)

Six studies found no clinically importance difference between Pregabalin and placebo in rates of nausea up to twenty four hours postoperatively (6 studies, n=353, moderate quality evidence)

Seven studies found no clinically important difference between Pregabalin and placebo in vomiting rates twenty four hours postoperatively (7 studies, n=425, high quality evidence)

Two studies showed no clinically important difference between Pregabalin and placebo for rates of nausea and vomiting postoperatively (2 studies, n=176, low quality evidence)

One study which assessed sedation between Pregabalin and placebo under six hours postoperatively which not estimable (1 study, n=60, low quality evidence)

Two studies found no clinically important difference between Pregabalin and placebo in sedation twenty four hours postoperatively (2 studies, n=106, low quality evidence)

Two studies found no clinically important difference between Pregabalin and placebo in the Ramsay Sedation score under six hours postoperatively (2 studies, n=180, moderate quality evidence)

One study assessing the Ramsay Sedation score from six to twenty four hours found no clinically important difference between Pregabalin and placebo (1 study, n=90, moderate quality evidence)

Two studies found a clinically important harm with Pregabalin for dizziness under six hours postoperatively compared to placebo (2 studies, n=168, moderate quality evidence)

Five studies showed no clinically important difference between Pregabalin and placebo in dizziness rates up to twenty four hours postoperatively (5 studies, n=293, low quality evidence)

Four studies found no clinically important difference between Pregabalin and placebo in postoperative pruritus (4 studies, n=266, moderate quality evidence)

Two studies assessing urinary retention postoperatively found no clinically important difference between Pregabalin and placebo (2 studies, n=136, low quality evidence)

Two studies found no estimable difference when assessing respiratory depression postoperatively between Pregabalin and placebo (2 studies, n=102, low quality evidence)

One study found no clinically important difference between Pregabalin and placebo in headache under six hours postoperatively (1 study, n=60, low quality evidence)

Three studies found no clinically important difference between Pregabalin and placebo in headache from six hours to twenty four hours postoperatively (3 studies, n=162, low quality evidence)

Two studies showed no clinically important difference between Pregabalin and placebo in postoperative somnolence 2 studies, n=127, low quality evidence)

Length of stay

One study showed no clinically important difference between Pregabalin and placebo for length of stay (1 study, n=37, low quality evidence)

Gabapentin vs Pregabalin

Pain

Three studies showed no clinically important difference between Gabapentin and Pregabalin for pain scores up to six hours postoperatively (3 studies, n=157, very low quality evidence)

Four studies found no clinically important difference between Gabapentin and Pregabalin for pain scores up to twenty four hours postoperatively (4 studies, n=178, high quality evidence)

Rescue medication

One study found a clinically important benefit with Gabapentin for opioid consumption compared to Pregabalin up to six hours postoperatively (1 study, n=72, moderate quality evidence)

Seven studies showed no clinically important difference between Gabapentin and Pregabalib for the dose of opioid consumed up to twenty four hours postoperatively (7 studies, n=372, very low quality evidence)

Adverse events

Three studies showed no clinically important difference between Gabapentin and Pregabalin for postoperative sedation (3 studies, n=170, low quality evidence)

One study found no clinically important difference between Gabapentin and Pregabalin in rates of respiratory depression, nausea & vomiting, urinary retention, headache and pruritus (1 study, n=60, low quality evidence)

Five studies showed no clinically important difference between Gabapentin and pregabalin for postoperative nausea rates (5 studies, n=279, low quality evidence)

Three studies found no clinically important difference between Gabapentin and pregabalin in postoperative dizziness rates (3 studies, n=147, low quality evidence)

Two studies found no clinically important difference between Gabapentin and Pregabalin for rates of postoperative somnolence (2 studies, n=97, low quality evidence)

Length of stay

One study found no clinically important difference in length of stay between Gabapentin and Pregabalin (1 study, n=37, moderate quality evidence)

Gabapentin vs Opioid

One study found no clinically important difference between Gabapentin and an opioid for pain score up to six hours, pains score up to twenty four hours, dose of opioid consumed at twenty four hours, sedation, nausea and vomiting and respiratory depression (1 study, n=306, moderate to very low quality evidence)

Amitriptyline vs placebo

One study assessing length of hospital stay found a clinically important harm with amitriptyline compared to placebo (1 study, n=24, low quality evidence)

Evidence not suitable for GRADE

Gabapentin vs Placebo

Pain

Six studies showed a trend towards benefit with Gabapentin for median pain score under six hours compared to placebo (6 studies, n=399, high risk of bias)

Three studies showed no notable difference between Gabapentin and placebo when assessing pain score from six to twenty four hours postoperatively (3 studies, n=209, low risk of bias)

One study showed no notable difference between Gabapentin and placebo when assessing the pain score using the McGill pain score (SF-MPQ-2) (1 study, n=50, high risk of bias)

Rescue medication

Two studies showed a trend to benefit for Gabapentin in the median dose of opioid consumed under six hours postoperatively compared to placebo (2 studies, n=169, high risk of bias)

One study showed a trend to benefit for Gabapentin for the median dose of opioid consumption from six to twenty four hours (1 study, n=99, high risk of bias)

Adverse events

One study showed a trend to harm with Gabapentin using the Richmond sedation score compared to placebo (1 study. n=50, high risk of bias)

One study showed a trend to benefit with Gabapentin in anxiety scores compared to placebo (1 study, n=50, high risk of bias)

One study showed no notable difference between Gabapentin and placebo in measuring somnolence under six hours postoperatively and from six to twenty four hours postoperatively (1 study, n=80, high risk of bias)

One study showed a trend to benefit with Gabapentin when measuring somnolence overall, compared to placebo (1 study, n=82, low risk of bias)

Pregabalin vs Placebo

Pain

Three studies showed a trend to benefit with Pregabalin in pain scores under six hours postoperatively compared to placebo (3 studies, n=232, high risk of bias)

One study showed a trend to benefit with Pregabalin from the area under the curve when assessing pain at rest up to four hours postoperatively compared to placebo (1 study, n=52, high risk of bias)

Three studies showed a trend to benefit with Pregabalin for median postoperative pain from six hours to twenty four hours compared to placebo (3 studies, n=232, high risk of bias)

Rescue medication

Two studies showed a trend to benefit with Pregabalin when measuring the median dose of opioid used from six to twenty four hours postoperatively compared to placebo (2 studies, n=112, high risk of bias)

One study showed no notable difference between Pregabalin and placebo when using the Ramsay Sedation score (1 study, n=60, high risk of bias)

Gabapentin vs Pregabalin

One study showed a trend to benefit with Pregabalin for pain scores under six hours and from six to twenty four hours compared to Gabapentin (1 study, n=115, high risk of bias)

5.5.2 Health economic evidence statements

- No relevant economic evaluations were identified.

6 The committee's discussion of the evidene

Please see recommendations 1.6.1 – 1.6.14 in the guideline.

6.1 Interpreting the evidence

6.1.1 The outcomes that matter most

The committee agreed that the outcomes should be consistent across all the reviews and considered critical outcomes for decision making to be health-related quality of life, pain reduction, amount of additional medication use, and treatment related adverse events. Length of hospital stay, length of stay in intensive care unit, hospital readmission, symptoms scores and psychological distress and mental well-being were thought to be important outcomes.

The studies rarely reported quality of life or the important outcomes. Pain relief was the most frequently reported although this was measured differently across different reviews.

6.1.2 The quality of the evidence

The quality of evidence that was suitable for GRADE analysis ranged from very low to high. The majority of the evidence was graded at low quality. This was mostly due to risk of bias and imprecision.

Paracetamol

The evidence on the use of paracetamol alongside opioid analgesia ranged from very low to moderate quality. Although low quality due to imprecision, the committee agreed that the potential benefit of paracetamol in critical outcomes of pain relief and opioid use supported a recommendation.

Evidence of low to very low quality demonstrated the effect of IV paracetamol in perioperative pain management. The quality of the clinical evidence alone was insufficient to support a recommendation. As such, the committee attributed more weight to the cost-effectiveness data on IV paracetamol.

NSAIDs

The evidence available for the use of NSAIDs ranged from very low to high quality, with the majority of the evidence being of low quality. The committee also noted that the evidence not suitable for GRADE analysis was of high risk of bias. Despite the low quality evidence presented, the committee agreed that the evidence for the outcomes of pain and additional pain relief of NSAIDs over placebo supported a recommendation.

Opioids

The majority of the available evidence on IV versus oral opioid analgesia was of very low quality. The committee also noted that the evidence not suitable for GRADE analysis was of very high risk of bias. As such, the committee focused on select outcomes measures of pain, medication use and adverse events from moderate and low quality evidence for decision-making.

The quality of evidence on the route of opioid administration ranged from very low to high, with the majority of evidence being low due to imprecision. Although very low quality, the committee valued the critical outcome of pain relief highly for discussion around recommendation due to the number of included studies in the meta-analysed results.

Ketamine

Evidence of very low to high quality was included for the review on IV ketamine for post-operative pain management. A significant proportion of the evidence was of moderate or high quality, adding to the committee's confidence in the data.

Neuropathic Nerve Stabilisers

The quality of evidence for neuropathic nerve stabilisers ranged from very low to high quality. As such, the committee focused on select outcomes measures of pain and additional medication use from moderate and low quality evidence to support a recommendation.

6.1.3 Benefits and harms

Pain management planning

The committee emphasised that a pain management plan should be bespoke to the patient, considering personal preferences and made in the context of shared decision making. The committee also agreed that the adverse effects of the recommended pharmacological interventions should be discussed with the person and weighed for that particular person against the benefit provided. The plan needs to incorporate a number of different patient characteristics including comorbidities, renal and hepatic function, current medications and cognitive function. A pain management plan is applicable to people undergoing dental surgery. When selecting interventions the committee noted that is important to take into account potential benefits and harms, including long term impact. Pre-optimisation clinics will identify patients with difficult pain control and where psychological preparation may be required. The urgency of surgery may dictate which interventions are appropriate and their likely effectiveness. Strategies should also be tailored to the procedure and the expected level of pain that may result. Pain relief should aim to restore function and mobilisation. Patients who are not recovering as anticipated should be reviewed to prevent the development of chronic post-surgical pain.

Analgesia selection and the multimodal approach

The committee agreed that to promote the restoration of function postoperatively (commonly known as 'DrEaMing' Drinking, Eating and Mobilising) a multimodal approach to analgesia selection should be adopted. This approach is achieved by combining different analgesics that act by different mechanisms at different sites.

The committee noted that:

- All drugs have side effects. If you can minimise the amount of drug you give a person you minimise these and therefore minimise harm or potential risk of harm.
- In addition, many medications have what is known as 'synergy' when they are used with other medications. For a variety of pharmacological and chemical reactions and reasons. Synergy quite simply explained is the concept that 1+1=3. That is, when two medications are given together their overall net effect is compounded and significantly greater when given in combination than if given individually.
- This has notable benefits. Firstly, it attacks pain at separate sites and (different drug classes acting in different parts of the body) therefore gives greater overall net pain relief when using more than one drug. Secondly, it allows smaller doses of each drug to be given because the net overall effect combined is greater. Smaller doses of each individual drug may lead to fewer side effects and less risk of harm. Lastly, using multiple non-opioid drugs can allow for adequate pain relief without having to resort to opioids or high doses of opioids, reducing the risk of harm with potential opioid-related side effects, particularly opioid intolerance or opioid dependence.

This is established clinical practice in the UK and would be considered widespread practice internationally.

Paracetamol

The committee discussed the evidence on paracetamol administration for the management of postoperative pain.

Oral versus IV

A body of evidence comparing the clinical and cost-effectiveness of IV versus oral paracetamol administration was reviewed.

The evidence for early pain scores and pain scores at 24 hours showed no clinically important difference between IV and oral paracetamol.

The committee took note of the clinically important benefit for the number of participants requesting rescue medication and total opiate consumption at 24 hours with IV compared to oral paracetamol. This trend was found when assessing the opiate consumption (hydromorphine equivalents) from under 6 hours to 24 hours.

The evidence from one study showed a clinically increase in adverse events with IV paracetamol compared to oral paracetamol, when given as an infusion or a bolus.

The committee considered that the observed difference between oral and IV paracemtamol in rescue analgesia and totoal opioid consumption was too low to justify the vastly increased cost of IV paracetamol, particularly given the increased risk of adverse events with IV paracetamol.

IV Paracetamol + IV Opioid versus IV Opioid

The committee also reviewed the evidence on the administration of IV paracetamol alongside opioid analgesia.

The committee noted the evidence from one study assessing the difference in pain at conclusion of surgery, which showed a clinically important benefit in using paracetamol with opioid analgesia. However, the evidence from one study that reviewed the pain score 6 hours postoperatively and two studies that reviewed the pain score at 24 hours showed no clinically important difference when opioids with paracetamol were used compared to opioids alone.

One study reported the consumption of additional opioids 24 hours postoperatively. The evidence showed a clinically important benefit in the reduction of additional opioid consumption when using paracetamol with opioids. The committee agreed that while this was from a single study, the evidence was noteworthy.

The evidence from one study also showed a clinically important benefit in the reduction of postoperative adverse events in favour of a combination of paracetamol and opioids for postoperative pain relief.

Length of hospital stay and length of stay at the ICU were reported by studies and results discussed by the committee, however, for each outcome there was no clinically important difference between opioid and opioid and paracetamol treatment groups.

Overall, the evidence was limited and the committee were not confident they could make a recommendation tadding IV paracetamol. Taking into account this review with the oral paracetamol versus IV paracetamol review (which also included only a few studies and had mixed overall conclusions), the committee decided to recommend oral paracetamol and only IV paracetamol in specific situations.

NSAIDs

The committee discussed the evidence for using NSAIDs and COX-2 inhibitors for the management of postoperative pain.

The committee assessed the evidence from two overviews of Cochrane reviews and 11 Cochrane reviews, which showed a clinically important benefit in the short term use of NSAIDs or COX-2 inhibitors compared to placebo for achieving 50% pain relief and a reduction in the use of additional pain relief.

The committee noted that the overview of Cochrane reviews have been stabilised indicating that no updates of the included reviews are expected in the next five years, and no new data are likely to be available that change the conclusions for at least 10 years. The review will be reassessed for updating in 2027.

The committee also noted that there was no significant difference in the number of people experiencing one or more adverse events when using NSAIDs or COX-2 inhibitors compared to placebo. The committee noted that this finding was not unexpected given that the majority of the studies included in the reviews were assessing single dose interventions, and added that this cannot be extrapolated for the safety of longer term use of NSAIDs. For this reasons the committee recommended a single dose of NSAIDs.

Serious adverse events were noted to be rare. Across all of the reviews, serious adverse events in studies involving NSAIDs were reported for 10 participants, three taking ibuprofen, three taking placebo, two taking rofecoxib, one taking etodolac, and one taking naproxen. The nature of these adverse events was not reported. No deaths reported.

The committee were aware of the NICE guideline on hip fractures and excluded this population from the recommendation.

The committee also noted that the short term duration and nature of the procedures from the included studies meant that many of the outcomes relevant for this review could not be measured in the studies and were subsequently not reported in the Cochrane reviews.

No evidence was available for health-related quality of life, psychological distress and mental well-being, symptom scores, functional measures, length of stay in intensive care, length of stay in hospital or hospital readmission.

The committee agreed that there was a substantial amount of evidence demonstrating a clear benefit with NSAIDs or COX-2 inhibitors in improved management of pain, reduced rescue medication and no significant difference in adverse events. The committee felt that this also showed that NSAIDs and COX-2 inhibitors are safe for the short-term management of post operative pain and were confident in making a recommendation for their use within this setting.

Different NSAIDs

The evidence from a number of studies which compared NSAIDs to other NSAIDs (Naproxen versus Ibuprofen, Ketorolac versus Diclofenac, Diclofenac versus Ibuprofen) and NSAIDs compared to COX-2 inhibitors (Ketorolac versus Parecoxib, Diclofenac versus Celecoxib, Ibuprofen versus Celecoxib, Ketorolac versus Celecoxib) showed no clinically important difference for pain scores, additional opioid requirements, adverse events, length of stay or functional measures.

Overall, the committee recommended NSAIDs, particularly ibuprofen because it is less costly and there were no differences seen between NSAIDs and COX-2 inhibitors. NSAIDs are opioid sparing and there was an absence of adverse effects. As the use of intravenous NSAIDs is more costly and did not show a clinically important difference for various outcomes, the IV route of administration should be used only if the oral route is not possible.

Opioids

The committee discussed the evidence on opioid administration for the management of postoperative pain. A body of evidence comparing the clinical and cost-effectiveness of IV versus oral opioid administration was reviewed.

Oral versus IV

The evidence generally suggested no significant difference in pain relief between IV and oral opioid analgesia, although one study suggested poorer pain relief as measured by the global assessment score at 6-24 hours post-operatively.

The evidence for adverse events was inconsistent in its direction of effect. One study reported increased mean adverse events at 6 hours with IV opioid but no significant difference at 24 hours, another study demonstrated a clinical benefit with fewer adverse events with IV opioid, while a third showed no difference between IV and oral opioid for nausea and vomiting.

The committee also noted evidence suggesting a reduction in the amount of additional medication required with IV opioid, although a second study showed no significant difference in the number of patients requiring additional analgesia.

The committee agreed that there was no strong evidence showing a clear benefit with IV opioid over oral opioid. As such, the committee considered that the noted possible benefits in a reduction of totoal opioid consumption could not justify a recommendation for the routine use of IV opioid, particularly given the increased cost with IV route.

Epidural/PCA/spinal:

The committee also assessed the evidence on opioids as compared to neuraxial analgesic techniques. The majority of the evidence presented to the committee was comparing Patient Controlled Analgesia (PCA) to continuous epidural.

This evidence demonstrated a clinically important difference for post-operative pain within the first six post-operative hours in favour of continuous epidural. This trend favouring continuous epidural for post-operative pain was consistent up to 48 hours post-operatively. One study demonstrated a clinically important difference, again in favour of continuous epidural for total pain relief at both 24 and 48 hours post-operatively.

The committee noted the evidence from one study reviewing the amount of opioid consumption with continuous epidural and PCA, showing increased total dose with PCA. The committee agreed that while this was a consequence of treatment allocation, it was still noteworthy.

One study reported mental wellbeing six weeks post-operatively in patients allocated to one of the two treatment strategies. No difference was found between treatment arms for the number of people experiencing depression, however a clinically important difference was noted in the number of people experiencing post-traumatic stress in favour of continuous epidural.

A number of studies reported analgesia related adverse events following allocation to either PCA or continuous epidural. No clinically important difference was found for the likelihood of experiencing nausea or respiratory depression with either PCA or continuous epidural, but vomiting was more common in those allocated to receive PCA. This was observed by the committee to be a clinically important difference.

Functional score as measured by distance walked in six minutes at three and six weeks post-operatively was reported by one study. No clinical difference was found between people receiving PCA or continuous epidural.

Length of hospital stay, length of stay at the ICU and risk of hospital readmission were all reported by studies and results discussed by the committee, however, for each outcome

there was no clinically important difference between PCA and continuous epidural treatment groups.

The committee also reviewed the evidence from one study comparing the use of spinal anaesthesia and PCA. The study reported the risk of hospital readmission following discharge and complications including nausea, vomiting, and respiratory depression. For all outcomes there was no clinically important difference between the two treatment groups.

The committee agreed that there was some evidence of benefit with continuous epidural with improved pain management, on the whole across all of the outcomes, the net benefit was not significant with any one route of administration. As such, the committee considered that a choice of PCA or epidural should be and that people having major, complex open-torso surgery may benefit from the additional early pain relief provided by a continuous epidural.

Ketamine

The committee discussed the evidence for adding IV ketamine to IV opioid for the management postoperative pain.

The evidence demonstrated clinically important benefit with ketamine for pain management. A clinically important benefit was noted for the occurrence of moderate pain at four hours, severe pain at four hours, 'no pain' at 24 hours, and moderate pain at 24 hours. Pain described as very severe at 24 hours and number of occasions experiencing pain being ≥2 showed no clinically important difference.

A number of studies reported adverse events including mean nausea score at 24 hours, mean nausea score at 48 hours, nausea, vomiting, nausea and vomiting, and respiratory depression. All of these outcomes showed no clinically important difference

Administration of ketamine resulted in a clinically important benefit for the outcomes of additional opioid consumption at <6 hours and 24 hours, the number of people requiring additional opioids, morphine injections taken per person, number of rescue analgesic interventions, rescue meperidine consumption and rescue propofol. However, other additional opioid outcomes such as PCA fentanyl infusion rate at <6 hours, PCA fentanyl infusion rate at 24 hours, PCA use, requiring rescue NSAIDs, rescue paracetamol needed, rescue tramadol consumption, additional metamizole, and mean remifentail dose showed no difference between groups.

Psychological distress outcomes including global assessment score at three days and global assessment score at seven days showed clinically important benefit with ketamine. Although, delirium rating scale with moderate quality evidence showed clinically important harm. Mini mental state examination and dysphoria showed no clinically important difference.

Functional mobility outcomes including time to mobilisation, postoperative time to walk, physical performance and time to 90 degree knee flexion showed clinically important benefit with ketamine. Other functional measures such as time to maximal knee flexion, first steps and first transfer showed no clinically important difference, while one outcome of number of patients mobilised within 48 hours showed a harm with ketamine.

Length of hospital stay and length of stay in PACU showed no clinically important difference between intervention groups.

The committee noted the increased levels of delirium with ketamine, but agreed that overall ketamine provided a benefit, particularly with improved pain management and reduced opioid consumption. The committee agreed that these benefits will be particularly important in people with difficult to manage pain or those who have opioid sensitivity.

Neuropathic Nerve Stabilisers

The committee discussed a body of evidence comparing the clinical and cost effectiveness of neuropathic nerve stabilisers for the management of postoperative pain.

Gabapentin compared to placebo

The committee agreed that the evidence demonstrated a clinically important benefit for post-operative pain within the first six post-operative hours in with Gabapentin compared to placebo. This trend to benefit with Gabapentin was consistent at 24 hours although the difference was not seen to be clinically important.

Opioid consumption at 6 hours and 24 hours postoperatively also showed a clinically important benefit with Gabapentin.

A number of studies reported the occurrence of adverse events with Gabapentin or placebo. The committee noted evidence showing a clinically important benefit with Gabapentin for patients experiencing nausea and vomiting (combined outcome). A clinically important harm was also seen for post-operative dry mouth in those receiving Gabapentin. The committee agreed that there was no significant difference between the two groups for the remaining outcomes of.

The committee highlighted the significance of there being no clinically important difference between Gabapentin and placebo for the outcomes of dizziness and light headedness. The committee discussed that there is a concern in practice that neuropathic nerve stabilisers may cause dizziness and in turn reduce the person's capacity for mobilisation and subsequent speed of recovery. The committee suggested that these side effects may be caused by longer-term administration and noted that the evidence reviewed was from cases of single dose administration.

Pregabalin compared to placebo

A number of studies showed no clinically important difference in postoperative pain at six hours and 24 hours postoperatively between Pregabalin and placebo.

The committee assessed the evidence for the dose of opioid consumed postoperatively at 6 and 24 hours. This evidence demonstrated a clinically important benefit of Pregabalin over placebo at both time points.

The evidence for adverse events showed a clinically important benefit in the reduction of nausea at 24 hours, but also showed a clinically important harm with increased episodes of dizziness at 6 hours for Pregabalin, although there was no significant difference between groups at 24 hours postoperatively. There was also no clinically important difference for the adverse events of nausea at 6 hours, vomiting sedation, pruritus, urinary retention, respiratory depression, headache and somnolence.

Gabapentin compared to Pregabalin

The committee agreed that there was a suggestion of improved pain management with Gabapentin compared to Pregabalin within the first 6 hours post-operatively, although this difference was not considered to be clinically important.

The committee also noted an apparent reduction in post-operative opioid consumption with Pregabalin compared to Gabapentin. The committee did note that this finding was inconsistent with the comparison of Pregabalin or Gabapentin to placebo, which suggested a greater benefit over placebo with Gabapentin than with Pregabalin. The committee agreed that in their experience, the opioid sparing effect of neuropathic nerve stabilisers may be similar and did not have enough evidence to recommend one over the other.

There was no clinically important difference between Gabapentin and Pregabalin for the adverse events of sedation, respiratory depression, nausea and vomiting, dizziness, somnolence, urine retention, headache and pruritus.

Gabapentin compared to Opioid

The committee noted a clinically important reduction in the dose of opioid consumed with Gabapentin compared to opioids.

For the outcomes of pain scores at 6 or 24 hours, adverse events of sedation, nausea and vomiting and respiratory depression, there was no clinically importance difference between Gabapentin and opioids.

Amitriptyline compared to Placebo

The committee assessed the evidence from a single study which showed that the length of stay was longer with Amitriptyline over placebo.

Summary:

Paracetamol

There was limited evidence for the oral versus IV review and IV paracetamol with opioid review. From the oral paracetamol versus IV paracetamol review, the committee decided to recommend oral paracetamol in the first instance. Therefore, the committee also made the recommendation to not offer IV paracetamol unless the person cannot take oral medicine. The committee were not able to make a recommendation towards IV paracetamol with the addition of an opioid.

NSAIDS

The committee agreed that the evidence showed a benefit of giving NSAIDs over placebo. The committee noted no significant benefit of any one NSAID over another. So, a recommendation was made that in people who have no contraindications, oral ibuprofen should be given. IV NSAIDs may be indicated when the oral route is not an option. Traditional NSAIDs were less costly in comparison to COX-2 inhibitors, while IV interventions were more costly than oral interventions. So a recommendation was made to offer a traditional NSAID over a COX-2 inhibitor if the IV route is indicated.

The committee noted that the NICE guideline on hip fracture (CG124) has a do not use recommendation for NSAIDs. The decision was based on committee consensus of the risk of side effects particularly in the elderly. The recommendation in this guideline is to use NSAIDs in the perioperative period only thus limiting the potential for side effects to occur.

Opioids

The committee agreed that there was no significant evidence of difference in effect of opioid between the oral and IV routes. The committee also noted the higher cost of IV delivery and the potential limitations around mobilisation associated with IV PCA. Therefore, the committee made a recommendation that once the person is eating and drinking, an oral opioid should be offered when the pain is expected to be moderate to severe. If the oral route is not available and pain is moderate or severe, a choice should be considered between a PCA or a continuous epidural to relieve pain postoperatively. There was insufficient evidence to recommend one administration strategy over another.

Ketamine

The evidence showed a benefit of adding IV ketamine to an IV opioid for pain relief, therefore the committee made the recommendation in favour of a single dose of IV ketamine intraoperatively or postoperatively in addition to other types of pain relief.

Neuropathic nerve stabilisers

The committee made a recommendation for a single dose of Gabapentin in addition to other types of pain relief postoperatively if the pain is expected to be moderate to severe. The evidence showed there was a benefit of Gabapentin and Pregabalin over placebo. There was no evidence to suggest that a single dose of Gabapentin caused significant side effects. A direct comparison between Gabapentin and Pregabalin showed some superiority of Gabapentin for pain relief with some benefit of Pregabalin for opioid consumption.

6.2 Cost effectiveness and resource use

Pain (overarching)

No economic evidence was identified for each of the questions. Therefore unit costs were presented to help aid consideration of cost effectiveness.

Paracetamol

The committee indicated that the clinical data for oral and intravenous paracetamol showed similar effectiveness. Costs vary depending on the dose required; however, for a maximum daily dose of 4g IV paracetamol costs an average of £1.79. In addition to this there are disposable costs associated with an IV administration; therefore the total daily cost would be approximately £5. In comparison, oral paracetamol is very cheap with an average daily cost of £0.04 for 4g daily. The committee agreed that the clinical evidence did not show a benefit of using IV paracetamol and therefore it could not be considered cost effective. The only situation where IV paracetamol should be used is when the oral route is not available.

The committee stated that this recommendation would lead to a change in current practice, as IV paracetamol is used widely across the NHS for postoperative pain management. Due to the large difference in cost per patient, the recommendation will lead to cost savings for the NHS.

When the oral route is not available, IV paracetamol may have benefits and the committee were presented with evidence for IV paracetamol and IV opioids compared to IV opioids alone. Unit costs vary based on the dose required however, an estimate was calculated which showed that intravenous paracetamol and opioids was more expensive costing £5.81 per day. Intravenous opioids alone can cost £4.92 per day. The committee noted that there was some clinical benefit of administering IV paracetamol with opioids as one study demonstrated the amount of additional medication administered was lower in the paracetamol arm and reduced adverse events. Although paracetamol and opioids were more expensive, the clinical evidence suggested that adverse events and additional medication would be reduced which would at least partially offset these additional costs.

The committee highlighted that opioid sparing was an important issue for patients and that current practice has been moving towards administering paracetamol with opioids as part of a multimodal pain strategy. This evidence further supported the recommendation to offer paracetamol to all adults and to offer opioids when pain is moderate or severe.

NSAIDs

The committee noted that NSAIDs were clinically effective when compared to placebo. There is absence of evidence on some NSAIDs. However, there were no differences between the different NSAIDs and COX-2 inhibitors when they were compared.

The average cost of oral NSAIDs varied from £0.04 for ibuprofen and £0.11 for diclofenac. Intravenous NSAIDs result in an average daily cost of £4.19 including disposables. Celecoxib costs on average £0.04 per day and parecoxib which is administered intravenously costs approximately £14.57 per day including disposables. The committee noted that there was variation in current practice with centres offering different NSAIDs and Cox-2 inhibitors for

postoperative pain management. It was also noted that there was variation across the NHS regarding the administration of intravenous ketorolac and parecoxib.

As there was no clinical difference between the different NSAIDs, the committee agreed that ibuprofen should be offered as it is the cheapest intervention and offers the same benefit. Where the oral route is not available, the committee made a recommendation to use traditional intravenous NSAIDs as Cox-2 inhibitors are more expensive but showed no additional benefits. Due to the current variation in clinical practice, these recommendations should lead to cost-savings for the NHS.

Opioids

Oral opioids and intravenous opioids were compared and the clinical evidence suggested there was no significant benefit of one type of administration over the other. The cost of oral opioids is very low with an average cost of six commonly used oral opioids costing £0.24 per day. The cost of intravenous opioids can vary depending on whether they are administered by a nurse or through PCA. The average cost of nurse administered IV opioids is £4.92 but patient controlled analgesia can cost up to £21.10 per patient. The committee highlighted this cost may be an overestimate as a straight average was calculated however, there was no information to obtain a weighted average.

The clinical evidence did not show a difference in pain relief between the two types of administration. The committee highlighted that adverse events could lead to downstream costs however, the clinical evidence was inconsistent with studies showing different directions of effect. The committee indicated that current practice is to administer IV opioids and that patient controlled analgesia is commonly used even when the adult is able to eat and drink. The committee recommended oral opioids to adults as soon as they are able to eat and drink due to the clinical evidence showing no clear benefit of IV opioids and oral opioids being cheaper.

The committee evaluated the evidence comparing PCA to continuous epidural. The daily costs of PCA and continuous epidural vary depending on the dose required but estimates showed that continuous epidural was more expensive with PCA costing £21.10 and continuous epidural costing £27.97 per day. Also, the committee highlighted that there could be additional costs associated with epidurals as it can sometimes fail which can require staff time to readjust the epidural or remove it and set up a different administration method. Current practice has recently moved away from continuous epidurals however, there are certain situations where they are commonly used, especially when a person is unable to use PCA.

The committee highlighted that the evidence showed that continuous epidural was more effective for pain initially after surgery. There was also evidence from one study showing that people experienced less post-traumatic stress with continuous epidural. This could have a positive impact on the patient's quality of life shortly after surgery. One study showed that PCA resulted in additional opioid medication use which could lead to additional complications. Although continuous epidural showed some benefits, the committee agreed that there were areas where there was no clinical difference such as complications and readmissions. As a result, the committee recommended to consider both epidural or PCA for people undergoing major complex surgery. There are situations where continuous epidural may be more beneficial and these were considered such as major complex open-torso surgery and for people without capacity to use PCA. It was agreed that these recommendations would not lead to significant changes in practice.

Ketamine

The committee noted that administering IV ketamine in addition to opioids resulted in some clinical benefits. There were improvements in pain relief and ketamine use resulted in less

people requiring additional opioids or rescue medication. The average cost of using intravenous opioids is approximately £4.92 per day, but when using intravenous opioids along with ketamine this cost increases to approximately £7.75. Current practice varies across the NHS therefore, the committee noted that a recommendation could lead to a substantial resource impact. Although ketamine is expensive it can lead to savings as it reduces the need for additional opioids and rescue medication. It was discussed that ketamine would only be appropriate for people having surgery who are expected to have moderate to severe pain. The annual Perioperative Quality Improvement Programme Report 2018 showed that 31% of adults having major surgery experience moderate to severe pain in recovery, showing that ketamine would only be suitable in a third of major surgical cases.

Although ketamine resulted in some clinical benefits, the committee agreed that the evidence was not sufficient to support a strong recommendation for the use of ketamine, especially as it is more expensive. Therefore a recommendation to consider a single dose of IV ketamine to supplement other types of pain relief if the person's pain is expected to be moderate to severe was made.

Neuropathic nerve stabilisers

Unit costs of neuropathic nerve stabilisers are cheap with gabapentin costing £0.05 per day and pregabalin costing £0.12 per day.

Gabapentin in addition to opioids was compared to opioids alone. This showed that postoperative pain was reduced in the first six hours after surgery for those receiving gabapentin. Evidence showed that gabapentin was clinically effective in reducing nausea and vomiting and a reduction in additional opioid medication administered.

Pregabalin in addition to opioids was compared to opioids alone. Pregabalin reduced the amount of opioids consumed postoperatively but it also increased episodes of dizziness. The committee highlighted that the reduction in opioid consumption could offset the costs of pregabalin. However, issues with experiencing dizziness post-surgery were highlighted as this could potentially delay time to mobilisation which has an effect on recovery and can potentially increase length of stay.

Gabapentin and pregabalin were also compared to each other. The clinical evidence showed that gabapentin had some benefit of postoperative pain relief at six hours post-surgery but there was no difference in side effects. Gabapentin resulted in less opioid consumption post-surgery which the committee highlighted can result in savings as well as being beneficial to patients.

The committee highlighted that a recommendation for the use of neuropathic nerve stabilisers may lead to a change in practice as they are not regularly used in postoperative pain management.

The committee agreed that both gabapentin and pregabalin showed a clinical benefit over using opioids alone. As gabapentin had some benefits over pregabalin and is cheaper, a recommendation was made to consider a single dose of gabapentin to aid opioid sparing. Although this may lead to a change in practice, the committee agreed that it is unlikely to have a significant resource impact as a single dose of gabapentin is low cost and the cost of gabapentin would be offset by the savings in the reduction of downstream opioid consumption.

6.3 Other factors the committee took into account

The committee noted that solely relying on pain intensity scores to measure pain is not recommended, for example, the impact of pain on functioning also needs to be considered.

The committee noted that although paracetamol and NSAIDs can be administered rectally this was not considered to be appropriate for the majority of patients.

The committee noted significant variance within data on perioperative pain management with regard to the surgical interventions and participant populations. The committee reiterated that analgesic requirements will vary depending on the procedure and the individual, and this should be considered with any pain management plan. The committee noted that a number of studies in the Moore et al (2015) review were number people who had pain following dental surgery. In the experience and opinion of the committee the findings of the studies can be generalised to other procedure. The committee also highlighted that the efficacy of some analgesic interventions such as epidural administration can be highly skill-dependant.

The guideline committee highlighted the findings that NSAIDs are opiate sparing and also noted that they promote early mobilisation. Despite this they are not widely used. This is probably due to the risk of acute kidney injury particular in the elderly. However, these risks are highly unlikely with a single dose of NSAIDs.

The committee highlighted the importance of 'deprescribing' so that patients do not end up on unnecessary medications for pain in the long term. Furthermore, an opiod withdrawal plan would need to be considered if opioids were used in the longer-term. The committee were also aware of the NICE guideline in development on Safe prescribing and withdrawal management of prescribed drugs associated with dependence and withdrawal.

The committee highlighted that it was not possible to combine all of the interventions using a network meta-analysis due to diversity of patient populations and procedures. For example, some patients will never be able to take oral medications post-surgery and some people may be suitable for nerve stabilisers and not ketamine. For this reason, the recommendations are a 'tool box' approach to pain management rather than a stepped approach.

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