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Pharmacotherapy for the prevention of chronic pain after surgery in adults (Review)

Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I

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TABLE OF CONTENTS

[Intervention Review]

Pharmacotherapy for the prevention of chronic pain after surgery in adults

Luis Enrique Chaparro[1], Shane A Smith[2], R Andrew Moore[3], Philip J Wiffen[4], Ian Gilron[5]

[1]Anesthesiology Department, Hospital Pablo Tobon Uribe, Medellin, Colombia. [2]Department of Anesthesiology & Perioperative Medicine, Queen's University, Kingston, Canada. [3]Plymouth, UK. [4]Thame, UK. [5]Departments of Anesthesiology & Perioperative Medicine & Biomedical & Molecular Sciences, Queen's University, Kingston, Canada

Contact: Ian Gilron, gilroni@queensu.ca.

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ABSTRACT

Background

Chronic pain can often occur after surgery, substantially impairing patients' health and quality of life. It is caused by complex mechanisms that are not yet well understood. The predictable nature of most surgical procedures has allowed for the conduct of randomized controlled trials of pharmacological interventions aimed at preventing chronic postsurgical pain.

Objectives

The primary objective was to evaluate the efficacy of systemic drugs for the prevention of chronic pain after surgery by examining the proportion of patients reporting pain three months or more after surgery. The secondary objective was to evaluate the safety of drugs administered for the prevention of chronic pain after surgery.

Search methods

We identified randomized controlled trials (RCTs) of various systemically administered drugs for the prevention of chronic pain after surgery from CENTRAL, MEDLINE, EMBASE and handsearches of other reviews and trial registries. The most recent search was performed on 17 July 2013.

Selection criteria

Included studies were double-blind, placebo-controlled, randomized trials involving adults and evaluating one or more drugs administered systemically before, during or after surgery, or both, which measured pain three months or more after surgery.

Data collection and analysis

Data collected from each study included the study drug name, dose, route, timing and duration of dosing; surgical procedure; proportion of patients reporting any pain three months or more after surgery, reporting at least 4/10 or moderate to severe pain three months or more after surgery; and proportion of participants dropping out of the study due to treatment-emergent adverse effects.

Main results

We identified 40 RCTs of various pharmacological interventions including intravenous ketamine (14 RCTs), oral gabapentin (10 RCTs), oral pregabalin (5 RCTs), non-steroidal anti-inflammatories (3 RCTs), intravenous steroids (3 RCTs), oral N-methyl-D-aspartate (NMDA) blockers (3 RCTs), oral mexiletine (2 RCTs), intravenous fentanyl (1 RCT), intravenous lidocaine (1 RCT), oral venlafaxine (1 RCT) and inhaled nitrous oxide (1 RCT). Meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery

following treatment with ketamine but not gabapentin or pregabalin. Results with ketamine should be viewed with caution since most of the included trials were small (that is < 100 participants per treatment arm), which could lead to the overestimation of treatment effect.

Authors' conclusions

Additional evidence from better, well designed, large-scale trials is needed in order to more rigorously evaluate pharmacological interventions for the prevention of chronic pain after surgery. Furthermore, available evidence does not support the efficacy of gabapentin, pregabalin, non-steroidal anti-inflammatories, intravenous steroids, oral NMDA blockers, oral mexiletine, intravenous fentanyl, intravenous lidocaine, oral venlafaxine or inhaled nitrous oxide for the prevention of chronic postoperative pain.

PLAIN LANGUAGE SUMMARY

Systemic drugs for the prevention of chronic pain after surgery

Pain associated with surgery generally resolves within one to two weeks, however in some situations surgical patients are left with longstanding pain for months or even years after the surgical procedure. Researchers have studied the ability of various drug treatments to prevent the development of chronic pain after surgery and this systematic review evaluated published studies in this field. Available studies suggest a modest effect of ketamine, compared to placebo, for prevention of chronic pain after surgery, however small study size could lead to an overestimation of this effect. Studies of other drugs such as gabapentin and pregabalin did not suggest the same preventative effect. Additional large studies using improved research methods are necessary to more clearly identify treatments that are beneficial for preventing chronic postsurgical pain.

BACKGROUND

Description of the condition

Surgical procedures, as a cause of chronic pain, are unique among various kinds of tissue injury because the injury (for example surgical incision) is, to some degree, planned such that preincisional interventions are possible. This provides an opportunity to implement therapies that could prevent the development of the long-term, costly and devastating complication of chronic postsurgical pain. Studies that follow postsurgical patients over time suggest that various surgical procedures are associated with a high incidence of chronic postsurgical pain, including limb amputation (30% to 50%), breast cancer surgery (20% to 30%), thoracotomy (30% to 40%) and coronary bypass surgery (30% to 50%) (Perkins 2000). Furthermore, data from outpatient pain treatment clinics suggest that surgery is a contributor to chronic pain in 23% of patients (Crombie 1998).

Laboratory and clinical investigations have contributed to a better understanding of the mechanisms and pathogenesis of chronic postsurgical pain (Kehlet 2006). Although chronic postsurgical pain may not be exclusively neuropathic, clinical presentation (for example hyperalgesia, an exaggerated response to painful stimulus at or near the site of surgery; allodynia, pain following an innocuous stimulus at or near the site of surgery) and the association of chronic postsurgical pain with clearly nerve-injuring procedures (for example amputation) suggest that nerve injury is an important inciting event (Kehlet 2006). Laboratory studies of nerve injury have identified several mechanisms that contribute to persistent pain, including sensitization (leading to exaggerated pain responsiveness) of peripheral nociceptors (that is receptors preferentially sensitive to a noxious stimulus) and associated primary afferent neurons (nerves transmitting sensory information towards the central nervous system), new growth of neuromas (tumours arising in nerve tissue) on pain-sensing fibres (whose spontaneous activity can cause unexpected shooting pain) and sensitization of spinal cord and nerve cells in the brainstem and brain (again leading to exaggerated pain responsiveness).

Description of the intervention

The pharmacological mechanisms of these complex changes are such that they may be suppressed by several pain relieving drugs including opioids, cyclo-oxygenase inhibitors (for example non-steroidal anti-inflammatory drugs (NSAIDs)), local anesthetics and other sodium channel blockers (for example mexiletine), glutamate antagonists, anticonvulsant drugs (for example gabapentin) and antidepressant drugs (for example amitriptyline) (D'Mello 2008; Woolf 2000).

How the intervention might work

In considering the consequences of injury to nerves or other tissues, or both, it is important to note that the above pharmacological mechanisms may be involved in the induction or the maintenance, or both, of a persistent pain condition (Woolf 1991). This distinction is important because treatments that successfully suppress the induction of chronic postsurgical pain may serve to prevent its occurrence (that is they would only need to be administered during the induction period) whereas treatments which merely suppress maintenance will only reduce pain while the treatment is being actively administered.

Why it is important to do this review

In several animal studies, administration of different drugs in the setting of nerve or tissue injury has been reported to prevent the development of long-term pain-relevant sequelae (for example pain transmitter upregulation, hyperalgesia), including gabapentin (Cesena 1999), ketamine (Burton 1999), amitriptyline (McCarson 2005) and local anesthetic nerve blockade (Wen 2007). However, several human postoperative drug trials have failed to demonstrate such benefits (Hayes 2004; Nikolajsen 1997; Nikolajsen 2006), perhaps because of species differences, other complex issues related to the development of chronic pain (for example psychosocial issues, genetic predisposition and previous pain problems) and, most relevant to this review, differences in dose, duration and timing of the intervention.

There remains considerable uncertainty in this area leading to the focus of this review, which was to evaluate the efficacy of various drugs, administered systemically, for the purpose of preventing the development of, or transition to, chronic postsurgical pain. Given recently expressed uncertainty as to whether any systemic drugs have the potential to prevent chronic pain after surgery, the purpose of this broad review was to identify evidence from multiple trials suggesting that any specific drug prevents chronic pain after any specific surgical procedure.

Two systematic review protocols of narrower focus, recently published in the Cochrane Database of Systematic Reviews, are related to this protocol. Krisanaprakornkit 2007 propose to review pharmacological trials for the prevention of phantom limb pain and Andreae 2008 propose to review trials of local anaesthetics for the prevention of chronic pain after surgery.

OBJECTIVES

- The primary objective was to evaluate the efficacy of systemic drugs for the prevention of chronic pain after surgery by examining the proportion of patients reporting pain three months or more after surgery.
- The secondary objective was to evaluate the safety of drugs administered for the prevention of chronic pain after surgery.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind, placebo-controlled, randomized trials of one or more drugs administered systemically before, during or after surgery, or both, which measured pain (using a validated pain assessment instrument) three months or more after surgery. All considered trials were graded for risk of bias using the Cochrane risk of bias tool.

Types of participants

Participants of both genders, 18 years of age and older, undergoing planned surgical procedures involving tissue injury.

Types of interventions

Drugs administered immediately before, during or after the procedure by any dose, route or frequency.

Types of outcome measures

Patient-reported measure of pain three months or more after the procedure.

Primary outcomes

Proportion of participants reporting any pain at the anatomical site of the procedure or pain referred to the surgical site, or both (for example phantom limb pain, shoulder pain referred from the diaphragm etc.), three months or more after the procedure.

Secondary outcomes

1. Number of participants reporting moderate or severe pain at the anatomical site of the procedure six months or more after the procedure.
2. Number of participants dropping out of the study due to treatment-related adverse effects.

Search methods for identification of studies

Electronic searches

The following databases were searched for trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (from inception to July 17, 2013)*;*
2. MEDLINE (from inception to July 17, 2013);
3. EMBASE (from inception to July 17, 2013).

The search strategy used to search these databases can be seen in Appendix 1.

Searching other resources

Reference lists of identified published review articles on the subject of chronic pain after surgery were also searched for eligible clinical trials, as were the reference lists of any included studies or relevant excluded studies.

Data collection and analysis

Selection of studies

Studies were selected as per the criteria listed above.

Data extraction and management

Data extracted from each study included: study drug name(s), dose(s), route(s), timing and duration; surgical procedure; proportion of patients:

1. reporting any pain three months or more after surgery,
2. reporting at least 4/10 or moderate to severe pain three months or more after surgery, and proportion of participants dropping out of the study due to treatment-emergent adverse effects.

Data extraction was performed by LC and IG by reading each included study report and completing a data extraction form for each article.

Assessment of risk of bias in included studies

All considered studies were graded for risk of bias using the Cochrane risk of bias tool.

Measures of treatment effect

The primary comparison of interest was between study drug(s) and placebo. Comparisons of study drug(s) and any other active treatment comparators were also to be made. Studies were combined if they evaluated the same study drug(s) at roughly similar doses and durations of treatment (for example a study evaluating a single preoperative drug dose would not be compared to another study evaluating several weeks of treatment with the same drug). RevMan 5 was used to analyse the study data for binary outcomes. Sensitivity analyses were used to evaluate the robustness of a particular result by repeating primary analyses without any studies considered to be outliers with respect to study quality, drug dose and duration, or pain measurement scales.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed to compare the frequencies of positive trial results across differing:

1. surgical procedures,
2. timing of the intervention,
3. duration of intervention, and
4. study participants with respect to preoperative pain at the surgical site.

RESULTS

Description of studies

See the Characteristics of included studies and Characteristics of excluded studies tables for further information.

We identified 40 clinical trials that fulfilled the review inclusion criteria.

Results of the search

In July 2013, our systematic search identified 7640 citations, which were independently screened by two of the review authors (SS, LEC) based on the title and the abstract information. The first screening for obvious exclusions yielded 107 records that were retrieved and reviewed in full text. Finally, 40 studies fulfilled the inclusion criteria. See Figure 1.

Figure 1. Study flow diagram.

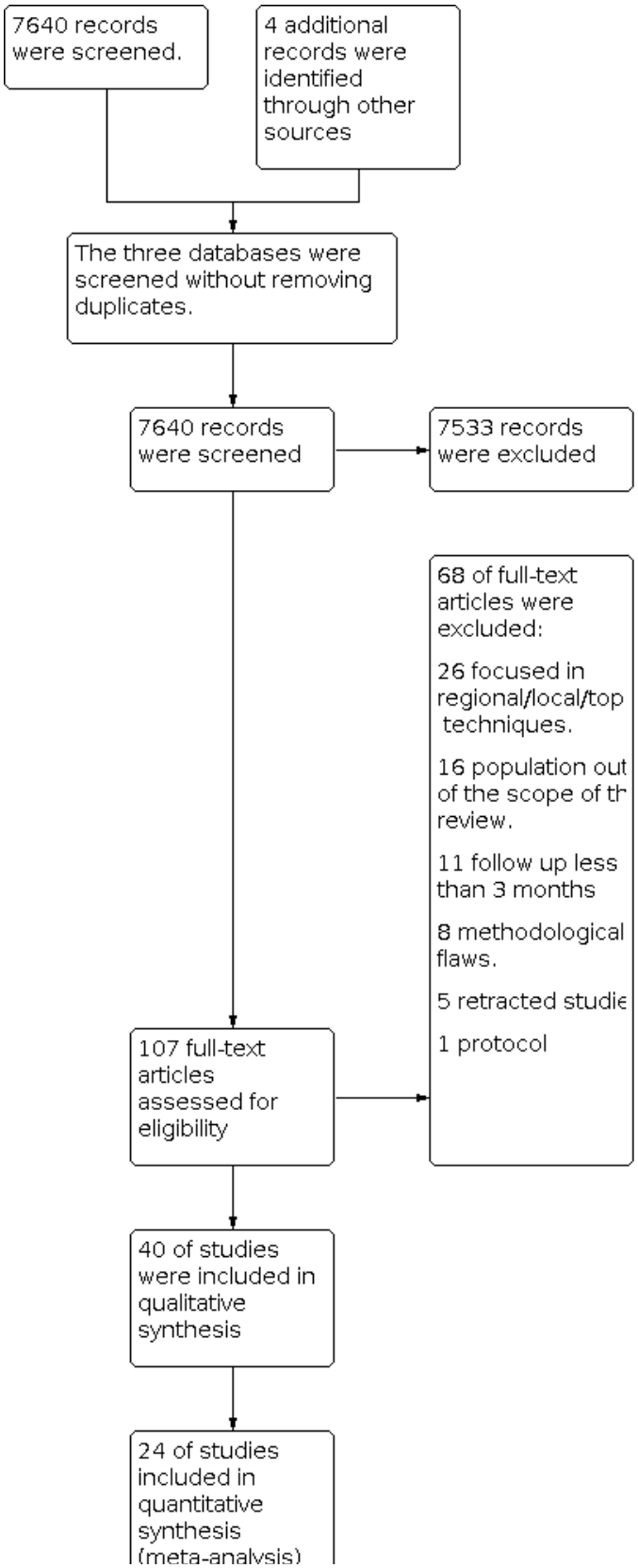
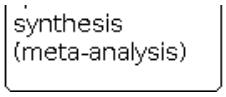


Figure 1. (Continued)



Our search for trials registered on the clinicaltrials.gov and controlled-trials.com databases yielded over 20 ongoing and unpublished studies. See Characteristics of ongoing studies.

Included studies

Study selection

We identified 40 papers that fulfilled the inclusion criteria of the review. Fourteen studies (1388 participants) used ketamine (Chaparro 2010; Crousier 2008; De Kock 2001; Duale 2009; Dullenkopf 2009; Hayes 2004; Katz 2004a; Malek 2006; Perrin 2009; Remerand 2009; Sen 2009a; Suzuki 2006; Sveticic 2008); one study evaluated (S)-ketamine (77 participants) (Spreng 2010). Ten studies (791 participants) evaluated gabapentin (Amr 2010; Brogly 2008; Clarke 2009; Fassoulaki 2002; Kinney 2011; Moore 2011; Nikolajsen 2006; Sen 2009; Sen 2009a; Ucak 2011). Five studies (509 participants) evaluated pregabalin (Burke 2010; Buvanendran 2010; Gianesello 2012; Kim 2010; Pesonen 2011). Three studies evaluated corticosteroids: one (50 participants) for dexamethasone (Bergeron 2009), another (219 participants) that compared methylprednisolone (Romundstad 2006) versus parecoxib and versus placebo, and a third one (36 participants) using hydrocortisone (Weis 2006). Two studies (166 participants) evaluated mexiletine (Fassoulaki 2001; Fassoulaki 2002). Two studies (932 participants) evaluated ibuprofen (Fransen 2006; Lakdja 1997). Single studies evaluated: amantadine (22 participants) (Eisenberg 2007); dextromethorphan (50 participants) (Ilkjaer 2000); lidocaine (36 participants) (Grigoras 2012); memantine (19 participants) Schley 2007; venlafaxine (150 participants) (Amr 2010); nitrous oxide (640 participants) (Chan 2011); and opioids (65 participants) (Karanikolas 2011).

Study design

This review included placebo-controlled studies except for one trial which compared several different active treatments (Karanikolas 2011). Several studies included a third arm or more for comparison: two studies included a dose response evaluation (De Kock 2001; Dullenkopf 2009); one study included four comparisons of low dose and high dose of intravenous and epidural ketamine (De Kock 2001). Two studies compared pre versus postincisional administration of the same medication: one study was performed with ketamine (Katz 2004a) and another one with gabapentin (Clarke 2009). We identified 3 head-to-head (comparative) studies that compared in a placebo-controlled fashion the administration of gabapentin versus ketamine (Sen 2009a), gabapentin versus venlafaxine (Amr 2010) and gabapentin versus mexiletine (Fassoulaki 2002). One head-to-head study compared methylprednisolone and parecoxib (Romundstad 2006). We identified one study that compared administration of oral mexiletine combined with regional block with local anesthetics versus each intervention alone (Fassoulaki 2001). A five arm trial compared several strategies for the administration of opioids, giving the medication by PCA or through an epidural catheter (Karanikolas 2011). Of the 40 included studies, trial sizes varied from eight (Perrin 2009) to 452 (Fransen 2006) participants per treatment arm.

Surgical procedures

Ten trials evaluated persistent pain after breast surgery: three with ketamine (Chaparro 2010; Crousier 2008; Malek 2006), one with gabapentin and venlafaxine (Amr 2010), one comparing a regional block versus mexiletine (Fassoulaki 2001), another from the same research group comparing gabapentin versus mexiletine (Fassoulaki 2002), one using ibuprofen (Lakdja 1997), one using methylprednisolone versus parecoxib (Romundstad 2006), and one using lidocaine (Grigoras 2012), one using amantadine (Eisenberg 2007). Six trials evaluated persistent pain after hip or knee arthroplasty: two using ketamine (Perrin 2009; Remerand 2009), one gabapentin (Clarke 2009), one pregabalin (Buvanendran 2010), one ibuprofen (Fransen 2006), and one dexamethasone (Bergeron 2009). Five trials assessed chronic pain after abdominal or pelvic surgery: three ketamine studies (De Kock 2001; Katz 2004a; Sen 2009a), one trial using gabapentin (Moore 2011), and one clinical trial using dextromethorphan (Ilkjaer 2000). Four randomized controlled trials (RCTs) assessed patients following limb amputation: one study of ketamine (Hayes 2004), one of gabapentin (Nikolajsen 2006), one of memantine (Schley 2007), and one of fentanyl (Karanikolas 2011). Chronic pain following thoracotomy was evaluated in three trials: two ketamine trials (Duale 2009; Suzuki 2006) and one study that used gabapentin (Kinney 2011). Three studies have evaluated persistent pain after heart surgery: one with pregabalin (Pesonen 2011), one with gabapentin (Ucak 2011), and one evaluating hydrocortisone (Weis 2006). Two studies evaluated persistent pain after spine surgery, both involving treatment with pregabalin (Burke 2010; Gianesello 2012). Long-term pain outcomes were reported in two thyroidectomy trials, involving treatment with gabapentin (Brogly 2008) or pregabalin (Kim 2010). Single analgesic trials that reported pain outcomes out to three months or longer involved other surgical procedures including inguinal herniorrhaphy (Sen 2009) and hemorrhoidectomy (Spreng 2010). Three trials involved a combination of different surgical procedures (Chan 2011; Dullenkopf 2009; Sveticic 2008).

Characteristics of participants: preoperative pain and analgesic use

Only seven of the 40 clinical trials only included patients that were free of pain or analgesic use before surgery (Brogly 2008; Chaparro 2010; Duale 2009; Eisenberg 2007; Ilkjaer 2000; Pesonen 2011; Sen 2009a). Patients taking any analgesic were excluded from 11 other trials (Amr 2010; Crousier 2008; Fassoulaki 2001; Fassoulaki 2002; Katz 2004a; Kim 2010; Lakdja 1997; Moore 2011; Romundstad 2006; Spreng 2010; Sveticic 2008). Patients taking more than 10 to 20 mg of morphine equivalent were excluded from four trials: two trials in major joint replacement surgery (Perrin 2009; Remerand 2009), one study in thoracotomy (Kinney 2011), and one in spine surgery (Gianesello 2012). Of note, we assumed that patients had at least mild preoperative pain in 10 trials given the indication for surgery: four studies involving joint replacement (Bergeron 2009; Buvanendran 2010; Clarke 2009; Fransen 2006), four studies for limb amputation (Hayes 2004; Karanikolas 2011; Nikolajsen 2006; Schley 2007), and two studies for decompressive spine surgery

(Burke 2010; Gianesello 2012). Information about preoperative pain or analgesic use was unclear or difficult to infer in seven studies (Chan 2011; De Kock 2001; Dullenkopf 2009; Grigoras 2012; Malek 2006; Sen 2009; Suzuki 2006; Ucak 2011; Weis 2006).

Drug interventions

Ketamine (14 trials) (Table 1): 12 of the 14 studies used a preincisional loading dose of ketamine, ranging from 0.15 to 1 mg/kg, plus an intraoperative infusion; two continued the infusion for the first 24 hours (Duale 2009; Remerand 2009), one for 48 hours (Malek 2006) and two additional studies maintained the ketamine infusion for three days (Hayes 2004; Suzuki 2006). One study mixed ketamine with morphine in a patient-controlled analgesia (PCA) device (Sveticic 2008). The cumulative dose of ketamine reached less than 1 mg/kg in 6/14 studies (Chaparro 2010; Crousier 2008; Dullenkopf 2009; Katz 2004a; Sen 2009a; Spreng 2010); 4/14 studies administered a cumulative dose of ketamine that ranged between 1 and 2 mg/kg (De Kock 2001; Malek 2006; Perrin 2009; Sveticic 2008) and four studies used a cumulative dosage > 2 mg/kg (Duale 2009; Hayes 2004; Remerand 2009; Suzuki 2006).

Gabapentin (10 trials) (Table 3): nine of the 10 studies administered a preincisional dose of gabapentin; this dosage ranged between 300 mg and 1200 mg; 6/10 studies evaluated a single dose of 600 mg (Clarke 2009; Kinney 2011; Moore 2011) or 1200 mg (Brogly 2008; Sen 2009; Sen 2009a); Of the other four multidose studies, one used gabapentin for two days in cardiac surgery (Ucak 2011), two evaluated 10 days of gabapentin administration in breast surgery (Amr 2010; Fassoulaki 2002) and one studied 30 days of gabapentin administration in an amputation trial (Nikolajsen 2006).

Pregabalin (five trials) (Table 3): all five pregabalin trials used a preincisional dose of 150 mg (Kim 2010; Pesonen 2011) or 300 mg (Burke 2010; Buvanendran 2010; Gianesello 2012) and at least one additional postoperative dose. The postoperative administration scheme for the drug varied across the trials from a single postoperative dose (Burke 2010; Kim 2010) to 14 days (Buvanendran 2010).

Corticosteroids (three trials): two of these three trials evaluated single preoperative doses, dexamethasone (40 mg) for total hip arthroplasty (Bergeron 2009) or methylprednisolone (125 mg) for augmentation mammaplasty (Romundstad 2006). In the third trial hydrocortisone was administered using a loading dose, intraoperative infusion and a tapering scheme up to the fourth postoperative day (Weis 2006). Further details about these studies are described in the Characteristics of included studies.

Ibuprofen (two trials): we found two ibuprofen trials, one that administered the analgesic for two weeks in patients undergoing total hip arthroplasty (Fransen 2006) and the other for only two days, including a preoperative dose, for breast surgery (Lakdja 1997). Further details about these studies are in the Characteristics of included studies.

Mexiletine (two trials): in two studies of patients undergoing breast cancer surgery (Fassoulaki 2001; Fassoulaki 2002), both trials had an active control arm, brachial plexus infiltration with ropivacaine (Fassoulaki 2001) or gabapentin (Fassoulaki 2002); mexiletine was administered for six or 10 days respectively.

Other drugs: we identified various other single drug trials, one study that evaluated amantadine administration for two weeks (Eisenberg 2007) and another that administered memantine for four weeks after traumatic amputation (Schley 2007); one study evaluated the intraoperative use of intravenous lidocaine (Grigoras 2012); one trial evaluated a single preoperative dose of dextromethorphan (Ilkjaer 2000) and another evaluated the intraoperative administration of nitrous oxide (70%) (Chan 2011). A single dose of parecoxib (40 mg) was administered as the active control arm of the aforementioned study of methylprednisolone (Romundstad 2006). Only one study using an antidepressant was identified (Amr 2010); venlafaxine was started before surgery and continued for 10 days at 37.5 mg/night. One five-arm study evaluated different strategies of intravenous versus epidural administration of fentanyl for two postoperative days (Karanikolas 2011). Further details about these studies are described in the Characteristics of included studies.

Outcome measures

Primary outcome

Any surgical site pain three or more months after surgery: the incidence of 'any pain' at any time point was reported in 26/40 studies (Chan 2011; Chaparro 2010; Clarke 2009; Crousier 2008; Duale 2009; Fassoulaki 2001; Fassoulaki 2002; Gianesello 2012; Grigoras 2012; Hayes 2004; Ilkjaer 2000; Katz 2004a; Kim 2010; Kinney 2011; Lakdja 1997; Malek 2006; Moore 2011; Nikolajsen 2006; Perrin 2009; Remerand 2009; Romundstad 2006; Schley 2007; Spreng 2010; Suzuki 2006; Sveticic 2008; Ucak 2011). Twenty-four trials collected this information using a 0 to 10 pain intensity scale (Bergeron 2009; Burke 2010; Clarke 2009; Duale 2009; Dullenkopf 2009; Fassoulaki 2001; Fassoulaki 2002; Fransen 2006; Grigoras 2012; Hayes 2004; Karanikolas 2011; Katz 2004a; Moore 2011; Nikolajsen 2006; Remerand 2009; Romundstad 2006; Schley 2007; Sen 2009a; Sen 2009; Spreng 2010; Suzuki 2006; Sveticic 2008; Ucak 2011; Weis 2006); 7/40 studies used a categorical pain scale for pain measurement (Chan 2011; Dullenkopf 2009; Gianesello 2012; Malek 2006; Nikolajsen 2006; Perrin 2009; Pesonen 2011). Additionally, only seven studies reported movement-evoked pain at three or more months after surgery (Amr 2010; Burke 2010; Dullenkopf 2009; Grigoras 2012; Pesonen 2011; Romundstad 2006; Spreng 2010).

Secondary outcomes

Moderate or severe surgical site pain six months after surgery: trials reporting data on this secondary outcome for this systematic review included three studies that followed up the patients at three months (Gianesello 2012; Nikolajsen 2006; Pesonen 2011); three studies that evaluated this outcome at six months (Buvanendran 2010; Malek 2006; Nikolajsen 2006); and one trial that included a one year follow-up (Gianesello 2012). Two trials quantified the incidence of mild or moderate pain, one at three months (Chan 2011) and the other at six months (Perrin 2009). Only one study reported the number of patients that persisted with severe pain (VAS > 5/10) (Chan 2011). A single study opted for the evaluation of pain control as poor, acceptable, or excellent (Dullenkopf 2009). The information on moderate to severe pain was retrieved on two occasions by the authors (Buvanendran 2010; Nikolajsen 2006).

Proportion of participants dropping out of the study due to treatment-related adverse effects: only 6/40 studies reported this outcome. One patient had to cancel the surgery due to severe sedation after 300 mg of pregabalin (Burke 2010); a similar situation

occurred with one patient that received pregabalin 300 mg before total knee arthroplasty (Buvanendran 2010); furthermore, one patient that received 600 mg of gabapentin before cesarean section dropped out from the study due to severe sedation (Moore 2011). In another gabapentin trial, in patients undergoing lower limb amputation, 2/23 in the active group and 2/23 in the placebo group dropped out from the study due to drug-related adverse events (Nikolajsen 2006). In another trial, 51/452 in the ibuprofen group versus 37/450 discontinued the treatment due to side effects or intolerance to the intervention (Fransen 2006). Of note, one trial that evaluated nitrous oxide reported that 217/640 patients were deceased before the follow-up (Chan 2011); 85% died secondary to cancer complications.

Other relevant outcome data: the incidence of pain or sensory abnormalities was reported at the three to four months time point by 24/40 studies (Burke 2010; Buvanendran 2010; Chan 2011; Crousier 2008; Duale 2009; Dullenkopf 2009; Eisenberg 2007; Fassoulaki 2001; Fassoulaki 2002; Gianesello 2012; Grigoras 2012; Ilkjaer 2000; Kim 2010; Kinney 2011; Moore 2011; Nikolajsen 2006; Pesonen 2011; Remerand 2009; Sen 2009a; Sen 2009; Spreng 2010; Suzuki 2006; Sveticic 2008; Ucak 2011); at six months by 21/40 (Amr 2010; Brogly 2008; Buvanendran 2010; Clarke 2009; De Kock 2001; Eisenberg 2007; Fransen 2006; Hayes 2004; Karanikolas 2011; Katz 2004a; Lakdja 1997; Malek 2006; Nikolajsen 2006; Perrin 2009; Remerand 2009; Schley 2007; Sen 2009a; Sen 2009; Suzuki 2006; Sveticic 2008; Weis 2006) and six studies reported outcomes at the 12 months time point (Bergeron 2009; Chaparro 2010; De Kock 2001; Gianesello 2012; Romundstad 2006; Schley 2007). A significant number of studies (15/40) reported pain-related descriptors or the number of chosen words from the McGill pain questionnaire (MPQ) (Amr 2010; Brogly 2008; Chan 2011; Chaparro 2010; Crousier 2008; De Kock 2001; Eisenberg 2007; Fassoulaki 2001; Fassoulaki 2002; Hayes 2004; Katz 2004a; Kim 2010; Moore 2011; Romundstad 2006; Suzuki 2006); the questionnaires were collected by mail or telephone interviews. Only a few studies opted for a clinical visit for physical examination and evaluation of sensory abnormalities (Buvanendran 2010; Crousier 2008; Duale 2009; Eisenberg 2007; Grigoras 2012; Ilkjaer 2000; Lakdja 1997). Validated scores for detection of neuropathic pain were used in three studies: one study opted for the neuropathic pain diagnostic questionnaire (DN2) score (Brogly 2008), another chose the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score (Buvanendran 2010) and a third one evaluated the pain using the neuropathic pain scale (Clarke 2009). Information about analgesic requirement was collected in 16/40 studies (Amr 2010; Buvanendran 2010; Chan 2011; De Kock 2001; Duale 2009; Eisenberg 2007; Fassoulaki 2001; Fassoulaki 2002; Fransen 2006; Hayes 2004; Nikolajsen 2006; Pesonen 2011; Remerand 2009; Romundstad 2006; Spreng 2010; Suzuki 2006). Functional outcomes or interference with activities of daily living by pain were evaluated in 18 studies (Bergeron 2009; Burke 2010; Buvanendran 2010; Chan 2011; Clarke 2009; Crousier 2008; Duale 2009; Fransen 2006; Gianesello 2012; Katz 2004a; Moore 2011; Perrin 2009; Remerand 2009; Romundstad 2006; Sen 2009a; Sen 2009; Ucak 2011; Weis 2006). Mood disorder scales were evaluated in three studies only (Clarke 2009; Gianesello 2012; Grigoras 2012).

Excluded studies

Given this review's exclusion criteria, trials evaluating regional anaesthesia techniques (Arcioni 2007; Bell 2001; Chiu 2008; Cohen 2006; Essving 2009; Essving 2010; Gupta 2006; Honigmann 2007; Jirarattanaphochai 2007; Kadic 2009; Kampe 2003; Katz 2004; Lambert 2001; Martin 2008; Morin 2005; Nikolajsen 2000; Obata 1999; Perniola 2009; Ryu 2011; Sanders 2009; Senturk 2002; Singh 2007) and that targeted injection therapies (Hartrick 2011; Wai 2010) or topical analgesia (Fassoulaki 2000) were excluded. We also excluded a clinical trial with one arm that combined topical analgesia and gabapentin (Fassoulaki 2005) since it was unknown how much the oral gabapentin effect contributed to the reported efficacy results of this multimodal intervention. Another study was excluded given that gabapentin was administered only to patients who developed moderate or severe pain (Elkaradawy 2012). Other studies were excluded because they had pain outcomes which were earlier than three months after surgery (Buvanendran 2003; Fassoulaki 2006; Fassoulaki 2007; Hartrick 2011; Kim 2011; Nissman 2008; White 2007). For more details please see the Characteristics of excluded studies table and Figure 1.

Risk of bias in included studies

Each study was assessed independently for risk of bias by two of the review authors (LC and IG) using the 'Risk of bias' tool (ROB) (Higgins 2011); 28/40 included studies had at least 4/7 items that qualified as low risk of bias. Several studies did not state the method for sequence generation or allocation concealment. Since most study medications were associated with recognizable adverse effects (for example sedation) in the acute setting, methods to prevent knowledge or evaluate (for example blinding questionnaires) the quality of blinding of outcomes assessors were not adequately addressed. Details are in the Characteristics of included studies table. Risk of bias assessments are presented in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

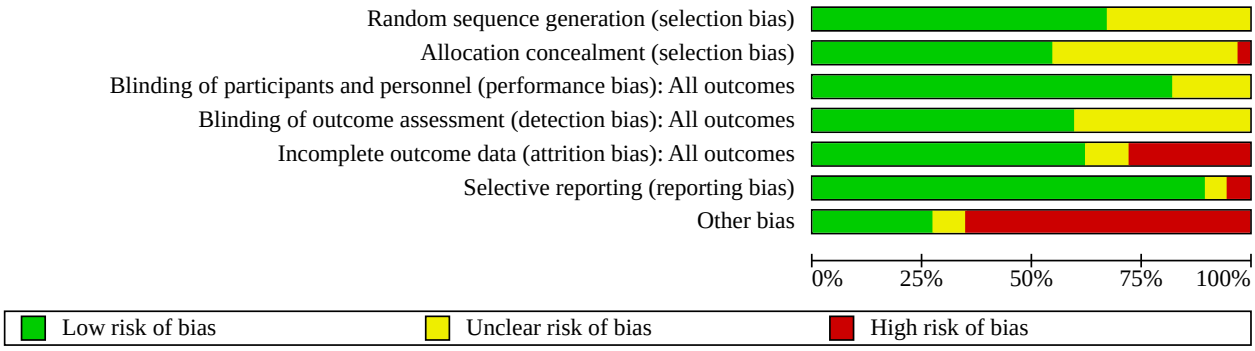


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

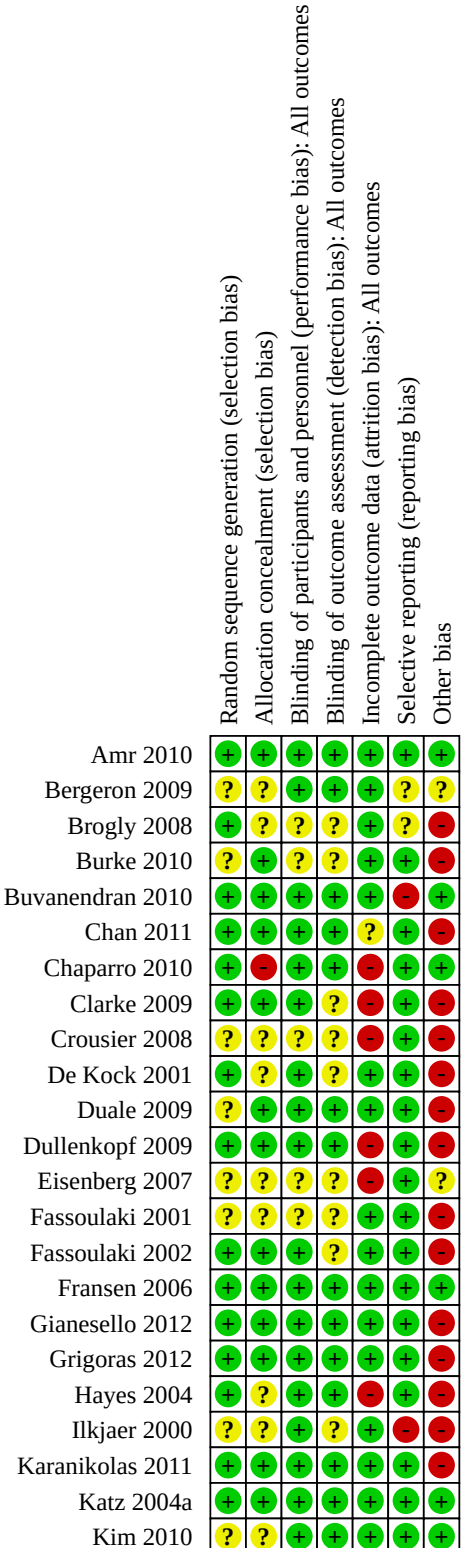
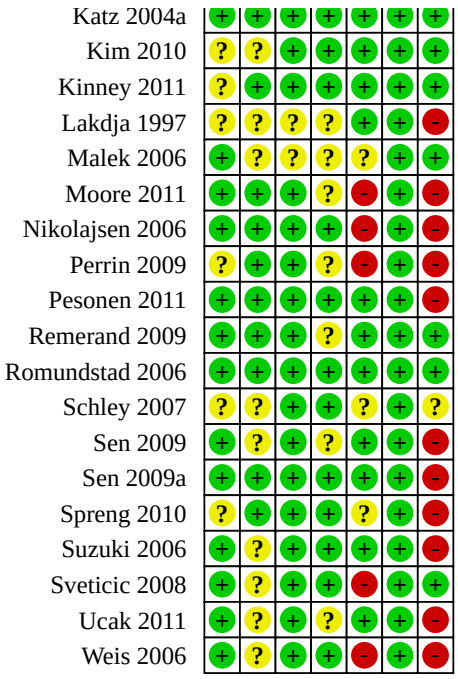


Figure 3. (Continued)



Allocation

Seventeen of the 40 included trials reported the method used to generate a random sequence and to keep the allocation concealed (Amr 2010; Buvanendran 2010; Chan 2011; Clarke 2009; Dullenkopf 2009; Fassoulaki 2002; Fransen 2006; Gianesello 2012; Grigoras 2012; Karanikolas 2011; Katz 2004a; Moore 2011; Nikolajsen 2006; Pesonen 2011; Remerand 2009; Romundstad 2006; Sen 2009a); and 15 additional studies (Brogly 2008; Burke 2010; Chaparro 2010; De Kock 2001; Duale 2009; Hayes 2004; Kinney 2011; Malek 2006; Perrin 2009; Sen 2009; Spreng 2010; Suzuki 2006; Sveticic 2008; Ucak 2011; Weis 2006) appropriately reported one or the other item.

Blinding

The vast majority of the trials reported how participants were blinded; however, 16/40 did not adequately described methods for blinding the outcomes assessors (see Figure 3).

Incomplete outcome data

Attrition bias was assessed as 'low risk' for studies where the dropout rate was below 20% (Bhandari 2005). Studies with higher dropout rates but including ITT analyses were assessed as 'unclear' or 'high risk of bias'.

Selective reporting

Although few studies indicated pre-trial registration on a clinical trial registry, all reported at least one of the outcomes that are considered to be clinically relevant (Dworkin 2005). This section was difficult to assess without access to the study protocol.

Other potential sources of bias

Given that the primary outcome was rarely the incidence of chronic pain, most of the included trials were underpowered for this particular outcome. This item was assessed as high risk in studies that had fewer than 50 participants per arm (Moore 1998).

Effects of interventions

Forty trials were included in this review.

Ketamine

Fourteen studies evaluating the perioperative effectiveness of ketamine were identified (Chaparro 2010; Crousier 2008; De Kock 2001; Duale 2009; Dullenkopf 2009; Hayes 2004; Katz 2004a; Malek 2006; Perrin 2009; Remerand 2009; Sen 2009a; Spreng 2010; Suzuki 2006; Sveticic 2008).

The studies are described in Table 1 in terms of the number of perioperative periods where the participants were exposed to ketamine: 1. preincisional loading dose; 2. intraoperative infusion; and 3. postoperative infusion (see Table 1). Three studies, one in thoracotomy (Duale 2009), a second one in amputation (Hayes 2004) and another one in total hip arthroplasty (Remerand 2009), administered ketamine in each of the periods of perioperative treatment; seven clinical trials used an incisional loading dose plus intraoperative infusion (Chaparro 2010; Crousier 2008; De Kock 2001; Katz 2004a; Perrin 2009; Sen 2009a; Spreng 2010); two studies started with an intraoperative infusion and continued the treatment for two (Malek 2006) or three (Suzuki 2006) postoperative days; only two studies limited the administration of ketamine to one of the three potential periods of treatment, one study used two different preincisional loading doses (Dullenkopf 2009) and one study administered ketamine mixed in the patient-controlled analgesia (PCA) device with morphine (Sveticic 2008).

A total cumulative dose was also calculated for each ketamine trial (see Table 1). A cumulative dose > 1 mg/kg was reached by eight out of the 14 aforementioned studies (De Kock 2001; Duale 2009;

Hayes 2004; Malek 2006; Perrin 2009; Remerand 2009; Suzuki 2006; Sveticic 2008).

Only two ketamine studies did not report the outcomes of interest for this review (Dullenkopf 2009; Sen 2009).

Ketamine three month postoperative pain outcome

Five studies reported the incidence of pain at three months: one study in patients undergoing thoracotomy (Suzuki 2006); one study in breast surgery (Crousier 2008); two studies in major orthopaedic procedures (Remerand 2009; Sveticic 2008); and one study using (S)-ketamine reported the incidence of pain at three months after inguinal herniorrhaphy (Spreng 2010). A sixth study in thoracotomy patients evaluated pain outcomes at four months after surgery (Duale 2009), which we chose to exclude from this meta-analysis given the time point difference of one month. The overall effectiveness risk ratio showed a non-significant effect for ketamine compared to placebo (odds ratio (OR) 0.74, 95% confidence interval (CI) 0.45 to 1.23). A subgroup analysis based on duration of treatment suggested a significant effect of ketamine compared to placebo (OR 0.37, 95% CI 0.14 to 0.98) for studies evaluating ketamine treatment for longer than 24 hours compared to studies of less than 24 hours of ketamine treatment that, together, resulted in a non-significant effect of ketamine compared to placebo (OR 0.82, 95% CI 0.4 to 1.7).

Ketamine four month postoperative pain outcome

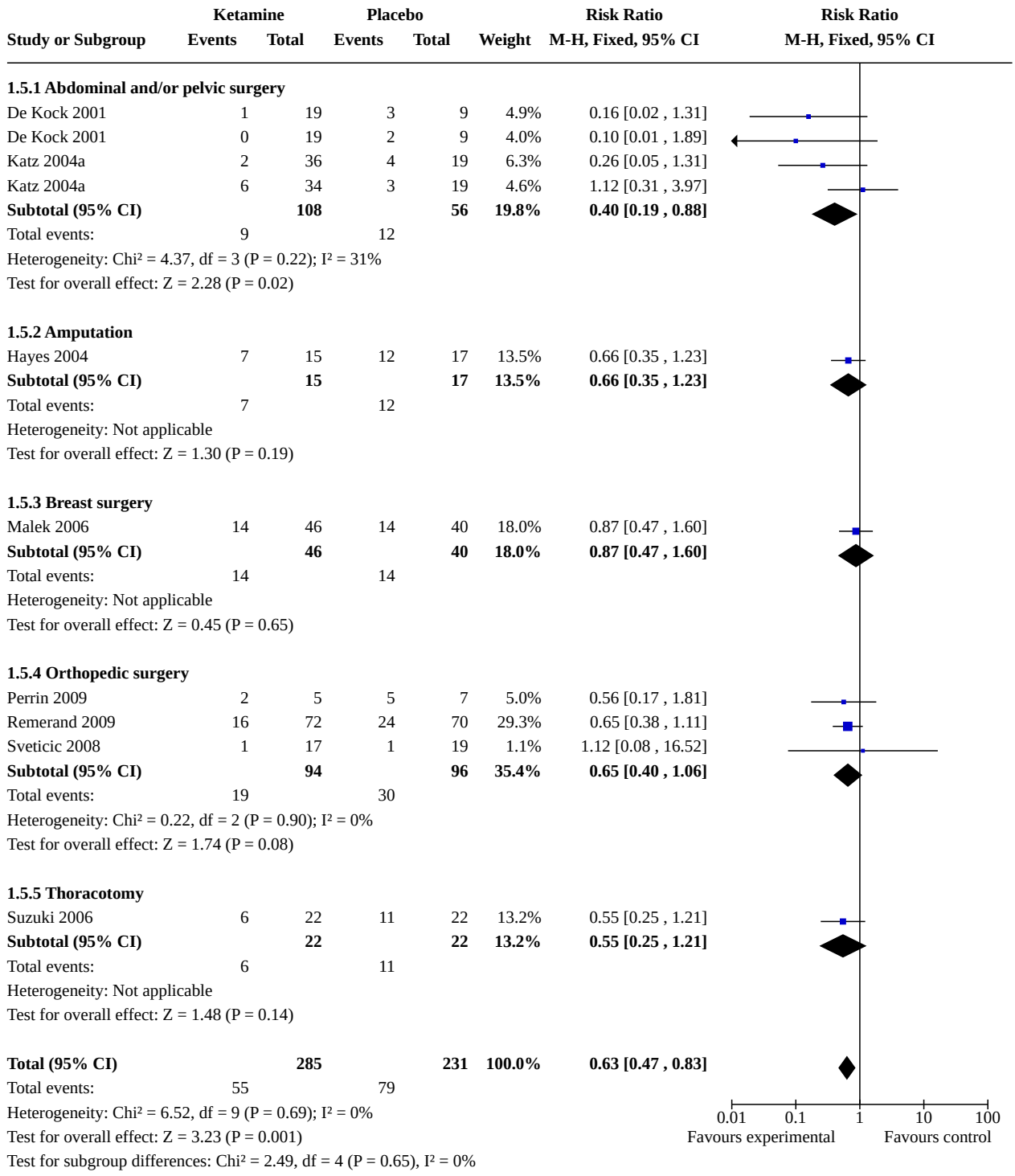
Only one study reported the incidence of pain at four months (Duale 2009). The data reported showed no difference between groups and corresponded with the item 'ongoing pain' from a validated tool called the Neuropathic Pain Symptom Inventory, reported by the authors.

Ketamine six month postoperative pain outcome

Eight trials reported the incidence of pain at six months: two trials in joint replacement surgery (Perrin 2009; Remerand 2009); one in amputation surgery (Hayes 2004); one in thoracotomy (Suzuki 2006); one in mixed orthopedic procedures (Sveticic 2008); one in rectal carcinoma resection (De Kock 2001); one in breast surgery Malek 2006; and one in radical prostatectomy (Katz 2004a).

Eight clinical trials reported the incidence of pain (any) at six months follow-up (De Kock 2001; Hayes 2004; Katz 2004a; Malek 2006; Perrin 2009; Remerand 2009; Suzuki 2006; Sveticic 2008); the overall effectiveness risk ratio showed a significant difference favouring ketamine compared to placebo (OR 0.50, 95% CI 0.33 to 0.76) (see Figure 4). A subgroup analysis based on duration of treatment failed to support a significant effect of ketamine compared to placebo (OR 0.58, 95% CI 0.31 to 1.09) for studies evaluating ketamine treatment for longer than 24 hours, whereas studies of less than 24 hours of ketamine treatment surprisingly did result in a significant effect of ketamine compared to placebo (OR 0.45, 95% CI 0.26 to 0.78).

Figure 4. Forest plot of comparison: 1 Ketamine versus placebo comparisons, outcome: 1.5 Incidence of any pain at 6 months (all studies).



Three studies reported the incidence of moderate to severe pain (Hayes 2004; Malek 2006; Remerand 2009); the overall effectiveness risk ratio showed a significant difference favouring ketamine compared to placebo (risk ratio (RR) 0.44, 95% CI 0.20 to 0.93). Two of the three trials administered ketamine during the perioperative periods (Hayes 2004; Remerand 2009); the other trial started an intraoperative infusion that continued for two days after surgery (Malek 2006). The number needed to treat for patients that should receive ketamine to avoid one case of moderate to severe pain at six months was 10.83 (95% CI 5.69 to 109).

Ketamine 12 month postoperative pain outcome

Two studies reported the incidence of pain at 12 months. One of the studies compared high and low doses of intravenous and epidural ketamine versus placebo in patients undergoing rectal carcinoma resection (De Kock 2001); 92/100 patients were successfully contacted and 3/17 patients in the control group reported persistent pain versus none (0/37) in the intravenous ketamine groups; one patient in each epidural ketamine group (2/38) reported chronic pain (De Kock 2001). The other study was performed in women undergoing augmentation mammaplasty (Chaparro 2010). Only 50/106 patients could be contacted by a telephone call. None of the participants reported moderate or severe pain, however 3/25 patients in the ketamine group versus 7/25 in the placebo group reported sensory abnormalities such as persistent hypoesthesia and burning-like sensation around the surgical scar (Chaparro 2010). These studies were classified as heterogenous and a meta-analysis was not performed.

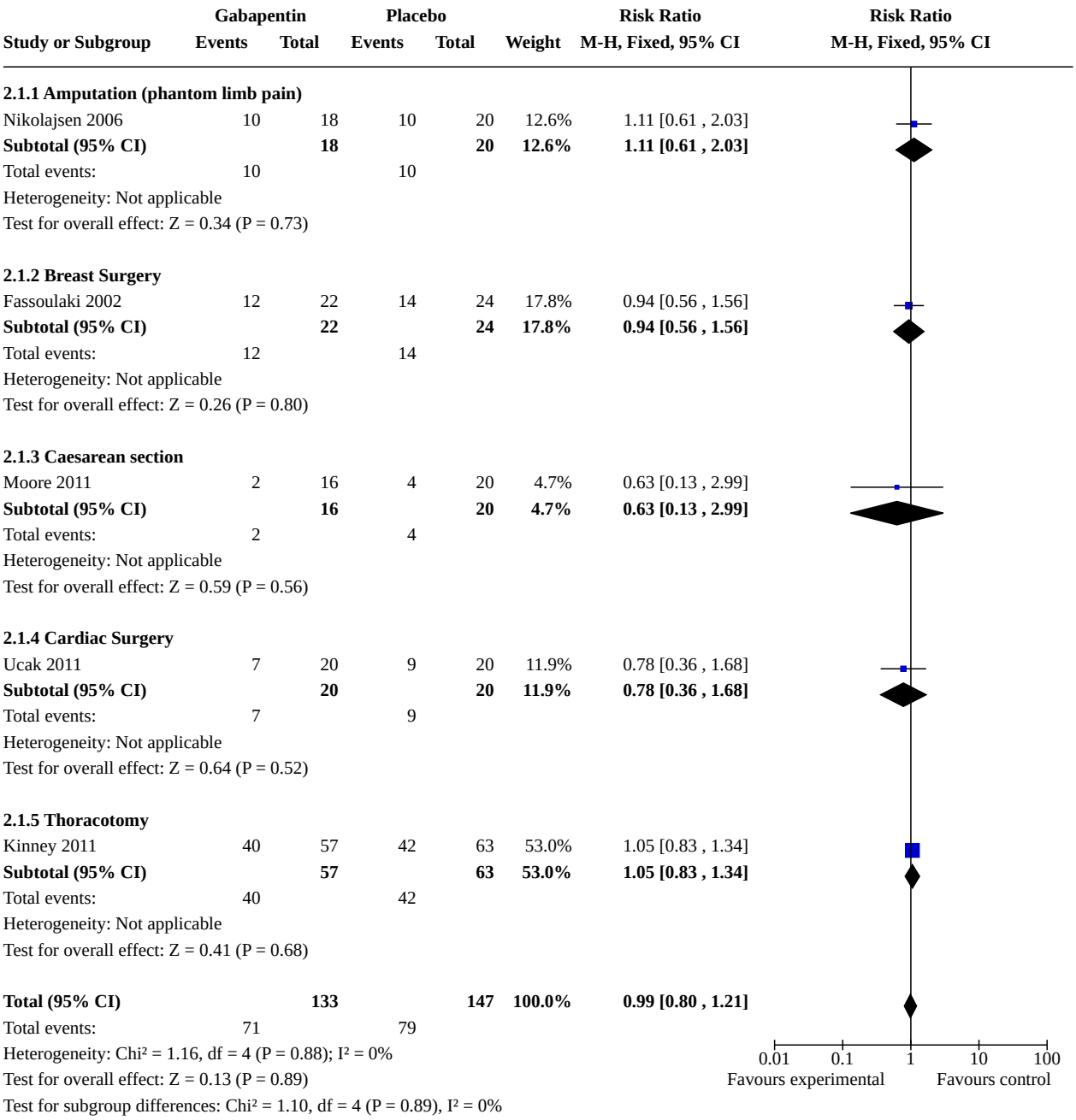
Gabapentin

We found 10 gabapentin clinical trials with long-term pain outcomes (Amr 2010; Brogly 2008; Clarke 2009; Fassoulaki 2002; Kinney 2011; Moore 2011; Nikolajsen 2006; Sen 2009; Sen 2009a; Ucak 2011). Table 2 describes trial features including surgery, preoperative and postoperative dosages, cumulative dose, as well as duration of gabapentin administration. One study administered gabapentin for 30 days (Nikolajsen 2006) in patients undergoing amputation. Two studies administered gabapentin for 10 days in breast surgery (Amr 2010; Fassoulaki 2002); however one of these trials did not report the incidence of pain but rather the median pain intensity score (Amr 2010) and was excluded from the meta-analysis. A single trial evaluated gabapentin administration in the setting of cardiac surgery (Ucak 2011). Six trials administered a single dose of gabapentin: one for inguinal herniorrhaphy (1200 mg single dose) (Sen 2009); one in the setting of abdominal hysterectomy (1200 mg single dose) (Sen 2009a); one arthroplasty study compared the administration of 600 mg of gabapentin in the preoperative period versus postoperative (Clarke 2009); one clinical trial reported the impact of gabapentin 600 mg after thoracotomy (Kinney 2011); another trial evaluated the long-term impact of 1200 mg of gabapentin after thyroidectomy (Brogly 2008); and finally, one trial was conducted in the setting of cesarean section (Moore 2011).

Gabapentin three month postoperative pain outcome

Four clinical trials reported the incidence of any pain at three months (Fassoulaki 2002; Kinney 2011; Moore 2011; Ucak 2011). In one study, which did not report the three month pain incidence in the publication, the authors provided these data upon our request (Nikolajsen 2006). Two studies were not included in the analysis given that they did not report the incidence of pain but rather a continuous pain score (Sen 2009; Sen 2009a). Together, none of the five studies with three month data demonstrated a significant difference over placebo (OR 0.97, 95% CI 0.59 to 1.59) (see Figure 5). Subgroup analyses based on duration of treatment failed to show any different results for studies evaluating less than 24 hours of gabapentin treatment compared to those evaluating longer than 24 hours of gabapentin treatment.

Figure 5. Forest plot of comparison: 2 Gabapentin versus placebo, outcome: 2.1 Incidence of any pain at 3 months (all studies).



Gabapentin six month postoperative pain outcome

Six out of 10 gabapentin trials followed the patients at six months. However, only two studies reported the primary outcome of the review, incidence of any pain (Clarke 2009; Nikolajsen 2006); neither of the two studies could demonstrate a significant difference with gabapentin over placebo. Three studies were not included in the analysis given that they did not report incidence, but a continuous pain score, and had no dichotomous outcomes such as incidence of moderate-severe pain (Amr 2010; Sen 2009; Sen 2009a). One study (Brogly 2008) reported the incidence of pain based on the scoring of the DN2 questionnaire, so the study was excluded from any meta-analysis.

Pregabalin

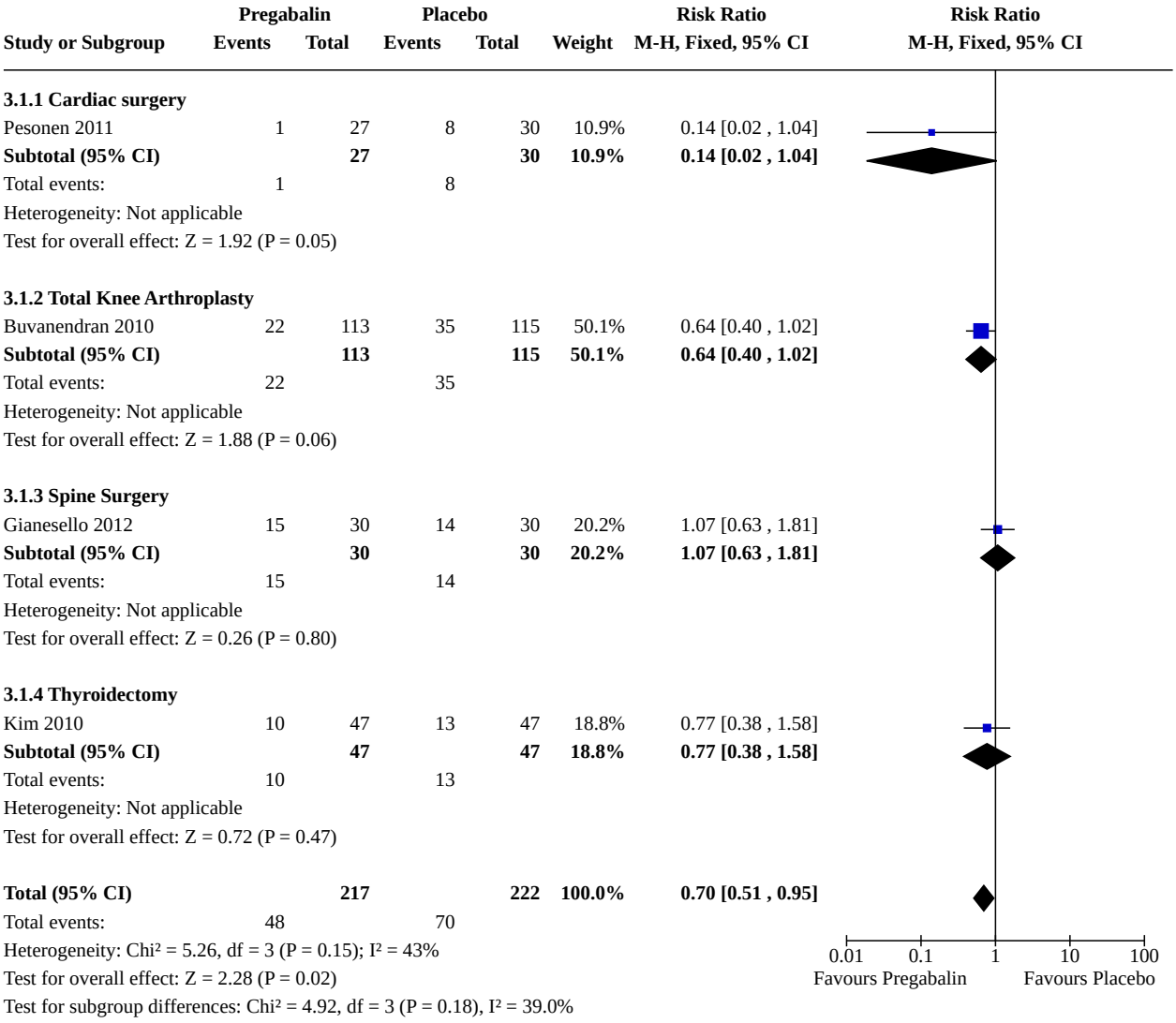
We identified five pregabalin trials with long-term pain outcomes (Burke 2010; Buvanendran 2010; Gianesello 2012; Kim 2010; Pesonen 2011). Table 3 describes the main characteristics of these studies, all of which involved more than one dose of study drug. Study medication was administered for at least two days in 3/5 trials (Buvanendran 2010; Gianesello 2012; Pesonen 2011). The preoperative dose was 150 mg (Kim 2010; Pesonen 2011) or 300

mg (Burke 2010; Buvanendran 2010; Gianesello 2012). The longest analgesic scheme opted for tapering pregabalin over two weeks for total knee arthroplasty (Buvanendran 2010). Pregabalin was studied in the setting of three major procedures: spine surgery, knee replacement, and cardiac surgery. A single trial evaluated the effects of pregabalin following thyroidectomy (Kim 2010).

Pregabalin three month postoperative pain outcome

Five clinical trials reported three month follow-up data (Burke 2010; Buvanendran 2010; Gianesello 2012; Kim 2010; Pesonen 2011) and four of them reported the incidence of any pain (Buvanendran 2010; Gianesello 2012; Kim 2010; Pesonen 2011). One study was excluded from the meta-analysis due to the lack of reporting on the incidence of pain but rather a continuous pain score (Burke 2010). Only one (Pesonen 2011) of these studies demonstrated a substantial benefit of pregabalin versus placebo leading to an overall significant effect of pregabalin over placebo (OR 0.60, 95% CI 0.39 to 0.93). However, assessment of heterogeneity yielded an I^2 of 28.5% (see Figure 6). Only one study evaluated less than 24 hours of pregabalin treatment so we did not perform any subgroup analyses according to treatment duration.

Figure 6. Forest plot of comparison: 3 Pregabalin versus placebo, outcome: 3.1 Incidence of any pain at 3 months follow-up (all studies).



Pregabalin six month postoperative pain outcome

Only one trial continued the follow-up for six months (Buvanendran 2010), in total knee arthroplasty. The authors were contacted and provided the outcome data upon request, which suggested a six month 'any' pain incidence of 15/113 for pregabalin versus 29/115 for placebo and a 'moderate-to-severe' pain incidence of 3/113 for pregabalin versus 13/115 for placebo.

Pregabalin 12 month postoperative pain outcome

One trial followed the patients for one year (Gianesello 2012) after major spine surgery. Based on our primary outcome, the study

could not demonstrate a significant benefit of pregabalin over placebo.

Corticosteroids

Three perioperative corticosteroid trials reported on long-term pain outcomes. One study evaluated the long-term analgesic effect of 40 mg of dexamethasone administered before total hip arthroplasty (Bergeron 2009). The study contacted, one year after surgery, 31/50 patients that were randomized. The study could not demonstrate any difference between groups for the main outcomes of pain intensity and function, measured by the Harris hip score. Another trial was developed to evaluate the long-term impact of a single preoperative dose of methylprednisolone (125 mg) for augmentation mammaplasty (Romundstad 2006). The study made contact with 175/219 randomized patients one year after surgery. This clinical trial showed no benefit in terms of pain scores, however it showed a significant difference favouring the steroid for the prevalence of hyperesthesia (Romundstad 2006). A third steroid trial was performed using a loading dose and four days of intravenous infusion of hydrocortisone after cardiac surgery (Weis 2006); the outcomes were measured at six months, when 28/36 patients were successfully contacted. The conclusions by the authors were that stress doses of hydrocortisone had a significant positive impact on chronic stress symptoms, including pain, and health-related quality of life. Heterogeneity between these trials, based on drug, follow-up timing and pain outcomes measured, precluded any possible meta-analysis.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Three perioperative NSAID trials reported long-term pain outcomes. One of these trials tested ibuprofen 400 mg before breast mastectomy plus four additional doses after the procedure (Lakdja 1997). Outcome assessment was planned at six months, when 28/30 patients were contacted; the authors concluded that ibuprofen had no significant impact on the control of dysesthesia or post-mastectomy pain syndrome (Lakdja 1997). A second ibuprofen trial was in patients undergoing total hip replacement (Fransen 2006); the primary outcomes were the changes in self-reported pain and function, measured using the Western Ontario and McMaster University arthritis index. Patients were contacted six to 12 months after surgery; the study could not demonstrate a significant impact of ibuprofen on the primary outcome (Fransen 2006). A third study included parecoxib as the active control arm of the methylprednisolone trial mentioned before (Romundstad 2006); a single dose of 40 mg of parecoxib made no difference versus placebo one year after surgery in patients undergoing augmentation mammaplasty (Romundstad 2006). Heterogeneity between these trials, based on drug, follow-up timing and pain outcomes measured, precluded any possible meta-analysis.

Other drugs

A comprehensive summary of the clinical trials developed for the following drugs is presented at Table 4.

Mexiletine: two clinical trials evaluated the impact of mexiletine (orally administered local anesthetic) on persistent pain after surgery. One of these studies (Fassoulaki 2001) had four arms, comparing the use of a regional block combined with mexiletine versus the interventions alone versus placebo. For the interest of this review, the study followed the patients for three months after surgery; the incidence of chronic pain or the mean pain scores did not differ between the four groups. However, the patients randomized to the combination reported less 'decreased sensation or hypoesthesia' at three months after surgery (Fassoulaki 2001). A second clinical trial (Fassoulaki 2002) used mexiletine (200 mg orally three times a day for 10 days) as an active control arm of a study that evaluated gabapentin for breast surgery (Fassoulaki 2002). As we mentioned before, the study followed the patients for three months after surgery. The incidence of chronic pain and the mean pain score had no statistical difference between groups. However, the authors reported a significant difference in burning sensation, equally favouring the administration of gabapentin or mexiletine over placebo (Fassoulaki 2002).

Lidocaine: one clinical trial (Grigoras 2012) evaluated the administration of intravenous lidocaine (bolus dose 1.5 mg/kg plus infusion 1.5 mg/kg/hour up to the first postoperative hour) in 36 patients that underwent breast cancer surgery. Long-term follow-ups were planned at three months after surgery. All patients were successfully contacted at three months after surgery: 2/17 patients in the lidocaine group versus 9/19 patients in the placebo group reported persistent pain after surgery; 0/17 in the lidocaine group versus 8/19 in the placebo group reported movement-evoked pain; the area of hyperalgesia was significantly larger in the placebo group at three months after surgery.

Amantadine: one clinical trial (Eisenberg 2007) evaluated the administration of amantadine sulfate (100 mg twice daily for 14 days starting the day before surgery) in 22 patients that underwent breast cancer surgery. Long-term follow-ups were planned at three and six months after surgery, and 17/22 patients were contacted at six months after surgery. All patients (9/9) in the amantadine group reported persistent pain after surgery versus 6/8 in the placebo group. The Short Form of the McGill pain questionnaire (SF-MPQ) was used for the follow-ups and no differences in the number of pain descriptors were found between groups. This study excluded patients that reported preoperative pain and participants were allowed to take opioids, anti-inflammatories or paracetamol as required.

Dextromethorphan: one clinical trial (Ilkjaer 2000) explored the impact of single dose dextromethorphan (150 mg orally before surgery) on pain after abdominal hysterectomy. All participants were free of pain before surgery. Long-term follow-up was performed at three months, and 45/50 randomized patients were successfully contacted and appointed for physical examination. A von Frey stimulation for evaluation of the area of hyperalgesia around the surgical wound showed no differences between groups, as well as the thresholds for pressure pain. Acute pain was managed with a PCA of morphine only.

Memantine: one study evaluated increasing doses of memantine (10 mg to 30 mg) administered during the first four postoperative weeks (Schley 2007) in patients undergoing traumatic amputation. All patients received a regional block for postoperative analgesia during one week. Patients were followed at one, six and 12 months after surgery. Pain prevalence was significantly lower in the memantine group compared to the placebo group at six, but not 12, months after surgery (Schley 2007).

Venlafaxine: a single clinical trial was developed to evaluate the potential role of antidepressants in the incidence of chronic pain after surgery. Venlafaxine was one of the two active arms of the clinical trial that evaluated the incidence of pain after

breast surgery (Amr 2010). This trial followed 150 patients during six months and no dropouts were reported. Outcomes measured included pain scores, at rest and movement-evoked, analgesic requirement and pain type incidence. The research group found that venlafaxine reduced the pain scores at six months compared to placebo and gabapentin. The incidence of burning and stabbing sensations was also reduced favouring venlafaxine over gabapentin or placebo (Amr 2010).

Nitrous oxide: a single clinical trial reported a secondary analysis to measure the impact of intraoperative 70% nitrous oxide in 640 patients undergoing numerous procedures. The research group followed the patients for three months and contacted 423/640 included patients; the rest of the patients died before the follow-up. The group reported the incidence of mild-moderate versus severe pain in the surgical site. They found a significant difference between groups, favouring the use of nitrous oxide. Of note, the benefit was even greater in those patients with severe pain. Patients with mild pain reported less pain-like sensations such as burning, squeezing, pressure, electric shock and movement-evoked pain among others (Chan 2011).

Fentanyl: a single opioid trial was identified that fulfilled the inclusion criteria for this review (Karanikolas 2011). This was a five arm study comparing standard regimens of preoperative, intraoperative and postoperative analgesia using PCA or epidural analgesia, or both, in 65 patients undergoing lower limb amputation. The four active groups were compared with intramuscular administration of meperidine; to keep the blinding, subcutaneous catheters plus second pumps were used across the study. A total of 56/65 randomized patients were contacted at six months after surgery. Based on the incidence of phantom limb pain, the study concluded that optimized analgesia with an epidural opioid or PCA started two days before surgery and continued up to the second day after surgery was better than intermittent administration of meperidine (Karanikolas 2011).

Ongoing studies

N-methyl-D-aspartate (NMDA) blockers: six clinical trials are evaluating the long-term analgesic impact of perioperative ketamine, one in patients undergoing major back surgery (NCT00618423); three studies in thoracotomy (NCT01243801; NCT01296347); one study in heart surgery (NCT01480765); and one study in women undergoing mastectomy (NCT00129597). One study is evaluating the analgesic efficacy of (S)-ketamine after major abdominal surgery (NCT01022840).

Gabapentin and pregabalin trials: we found numerous studies evaluating pregabalin, one study in heart surgery patients (NCT01480765); three studies in patients undergoing breast cancer surgery (NCT00852683; NCT01391858; NCT00631891); another study in thoracotomy (NCT00663962); and four studies in orthopedic surgery (NCT01359059; NCT00583869; NCT00905437; NCT00762099). One clinical trial is currently enrolling patients to test the effectiveness of gabapentin added to epidural analgesia for patients undergoing thoracotomy (NCT01116583).

Lidocaine: we identified a single study that is evaluating intravenous lidocaine in a placebo-controlled fashion for breast cancer surgery (NCT01204242).

Completed but unpublished studies

Ketamine: One trial of ketamine for prevention of long-term thoracotomy pain (NCT00224588) has been listed as completed on the clinicaltrials.gov website but has not yet been published.**Gabapentin and pregabalin trials**: four trials have been completed but not published, using pregabalin for thoracotomy (NCT00967135), inguinal hernia repair (NCT00551135), hysterectomy (NCT00468845) and total knee arthroplasty (NCT00442546).

DISCUSSION

Summary of main results

This review reveals a growing number of RCTs (40 included in this review) of perioperative systemic drug interventions that assess long-term pain outcomes (for example. ≥ three months after surgery). In many RCTs that appear to primarily evaluate the effect of treatment on early postoperative pain, the rationale for assessing long-term pain outcomes was often not provided and an expectation of treatment effect on long-term pain outcomes was not apparent. The observation that RCTs were conducted in various different surgical procedures, evaluating a wide variety of drug classes (for example NMDA antagonists, local anesthetics, anticonvulsants, antidepressants, NSAIDs, corticosteroids, opioids etc.) administered at a wide variety of treatment doses and durations (for example from a single preoperative drug dose to 30 days of treatment) reflect a current lack of understanding of the critical mechanisms and temporal aspects of development of chronic pain after surgery. Also, the frequently combined inclusion of study participants with and without preoperative pain represents a major challenge to the interpretation of postsurgical pain prevention trials.

The majority of the 40 published studies included in this review evaluated intravenous ketamine (14 RCTs), oral gabapentin (10 RCTs) and oral pregabalin (5 RCTs). Although we conducted several meta-analyses of these studies, results should be interpreted with caution given the clinical heterogeneity of studies with respect to surgical procedure, drug dose and treatment duration, and trial populations (for example with respect to presence of preoperative pain). Also, the diversity of specific outcome measures used (for example a 0 to 10 numerical rating scale for pain intensity versus composite neuropathic pain scales) and the pain assessment time points (for example three, four, six, 12 months) often limits the amount of data available for meta-analysis at any given time point.

Based on meta-analyses of available data from included placebo-controlled RCTs involving 194 to 285 ketamine-treated participants (depending on the specific meta-analysis), perioperative ketamine appears to reduce the incidence of pain at three months (if administered for more than 24 hours) and six months after surgery. As well as the incidence of any pain, results also indicated that ketamine decreased the incidence of moderate-to-severe pain at six months. However, most ketamine trials were small in size (that is < 100 participants per treatment arm), which could lead to overestimation of treatment effect.

Meta-analyses of gabapentin RCTs failed to demonstrate statistical significance upon comparison to placebo at three or six months. Although one meta-analysis of pregabalin RCTs indicated superiority over placebo for pain incidence at three months after

surgery, these results are largely driven by one cardiac surgery trial (27 to 30 participants per arm) with an extremely low incidence of pain in the pregabalin arm.

Overall completeness and applicability of evidence

As discussed above, included trials were diverse with respect to drug intervention and surgical procedure, and we did not identify more than one study for any single surgical procedure, drug intervention and follow-up time point. Also, it should be noted that measures of chronic postsurgical pain were not necessarily the primary outcomes for all included trials. That is to say, some of the trials were designed to evaluate early postsurgical pain whereas measures of pain at three months or later after surgery may have been secondary outcome measures. This raises the possibility of selective reporting bias, however we believe that all available results are worthy of consideration. For these various reasons, the applicability of the evidence is limited by the bounds of extrapolation of results across time points, drug doses and surgical procedures and caution is advised.

Quality of the evidence

The 40 included studies against placebo were of reasonably good quality with mostly low risks of bias related to treatment randomisation and blinding. Frequent risks of bias in many of these studies were related to small sample size (< 50 participants) (Moore 1998; Nuesch 2010). Reports of investigations which were insufficiently blinded or were uncontrolled were excluded as shown in the 'Characteristics of excluded studies' table.

Potential biases in the review process

Restriction of this review to double-blind RCTs limits the potential for bias, though the small size of most of the studies, their relatively short duration, and the high levels of withdrawals in some studies could all be sources of bias leading to greater treatment effect. Lack of access to potentially negative studies (for example studies #NCT00442546, #NCT00468845 and #NCT00551135 listed in the 'Ongoing studies' table), which remain unpublished, may be an important source of publication bias that our review strategy could not overcome.

Agreements and disagreements with other studies or reviews

In contrast to the conclusions of the present review, a recently published systematic review (Clarke 2012) concluded that gabapentin and pregabalin "are effective in reducing the incidence of CPSP". Some differences in that review compared to the present review which may explain the divergent conclusions include: 1) substantial heterogeneity by combining studies, in the same meta-analysis, of gabapentin and pregabalin, across different time points and pain assessment methods (for example pain intensity measures as well as composite neuropathic pain scales); 2) the unexplained lack of inclusion of an important negative gabapentin trial (Nikolajsen 2006); and 3) the inclusion of a positive 'gabapentin' trial (Fassoulaki 2005) which included the co-administration of local anesthetics together with gabapentin in the intervention arm only.

AUTHORS' CONCLUSIONS

Implications for practice

Comments below about the clinical implications of drug intervention studies included in this review refer only to the reported long-term pain prevention effects, that is just because evidence does not support efficacy for chronic postoperative pain prevention for a particular drug does not mean that it is not beneficial for the treatment of early postoperative pain.

Although our meta-analyses of ketamine seem to suggest population efficacy for reducing the prevalence of chronic postsurgical pain, results with ketamine should be viewed with caution since most of the included trials were small (that is < 100 participants per treatment arm), which could lead to overestimation of treatment effect. Therefore, additional large-scale trials are necessary to better determine which patient subgroups are likely to benefit from routine perioperative ketamine administration as well as to determine the optimal dosing regimen for chronic pain prevention.

Finally, available evidence does not support the efficacy of gabapentin, pregabalin, or other studied drugs for the prevention of chronic postoperative pain. Therefore, administration of these drugs specifically for the purpose of preventing chronic pain cannot be recommended.

Implications for research

Results of this review underscore the need for continued investigation into the etiology and pathogenesis of chronic postsurgical pain in order to better understand the inciting mechanisms (for example injury of nerves versus other tissues and other perioperative alterations in ascending and descending pain modulation) and novel pharmacological targets of prevention (Katz 2009; Kehlet 2006; Rappaport 2010).

Given the necessary resources to conduct well designed and conclusive pain prevention trials, the impact of future research would be maximized by focusing largely on surgical procedures associated with the highest prevalence of chronic postsurgical pain (for example amputation, thoracotomy, coronary artery bypass surgery and breast surgery).

The relevance of future chronic postsurgical pain prevention trials certainly relies on the use of clinically relevant outcome measures. In particular, pain outcomes should be assessed at multiple time points, for example from three months after surgery and forward to also include six, nine, 12 months and beyond as trial logistics allow. It would be optimal to include pain outcome measures that could be standardized (for example pain intensity on a 0 to 10 numerical rating scale or 0 to 100 visual analog scale) and, further, to define outcomes that can be dichotomized (for example 'any non-zero pain' and 'moderate-to-severe pain'). Other useful secondary outcomes at long-term follow-up time points include the use of or need for analgesics or other pain treatments as well as other functional (for example Brief Pain Inventory) and quality of life (for example SF-36) measures.

Determination of appropriate sample sizes for future prevention studies requires careful consideration and should be closely related to anticipated baseline rates of chronic postsurgical pain in the surgical population of interest (Kehlet 2010). Thus, studies

of surgical procedures associated with a lower prevalence of chronic postsurgical pain will need larger sample sizes in order to demonstrate statistically significant differences in outcome between control and intervention groups. Also, consideration must be given to clinically important differences in light of the safety and tolerability, cost and ease of use of the study intervention (Dworkin 2010). Avoidance of attrition bias requires attention and all attempts must be made to avoid loss to follow-up among study participants. Finally, stratification of study populations between those with and those without preoperative pain is crucial for proper interpretation of prevention trials and may affect statistical power and sample size determinations.

As suggested by this review, numerous pharmacological agents have been studied for the prevention of chronic postoperative pain. Most of these medications are known to be effective for the treatment of early postoperative pain but their efficacy in chronic pain prevention remains in question. The somewhat disappointing results from single-agent studies included in this review support recent suggestions by Dahl and Kehlet (Dahl 2011) that future, likely more complex studies should evaluate the potential for multimodal prevention strategies to more effectively prevent chronic postsurgical pain. This could include the combination of two or more drugs with different mechanisms of action (including at least one known to suppress central sensitization), the combination of regional analgesic techniques with the aforementioned pharmacological approaches, and possibly even the combination of nerve-sparing surgical techniques with the above analgesic strategies (Dahl 2011).

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REFERENCES

References to studies included in this review

Amr 2010 *{published data only}*

Amr YM, Yousef AA. Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. *The Clinical Journal of Pain* 2010;**26**(5):381-5. [PMID: 20473044]

Bergeron 2009 *{published data only}*

Bergeron SG, Kardash KJ, Huk OL, Zukor DJ, Antoniou J. Perioperative dexamethasone does not affect functional outcome in total hip arthroplasty. *Clinical Orthopaedics and Related Research* 2009;**467**(6):1463-7. [PMID: 19224304]

Brogly 2008 *{published data only}*

Brogly N, Wattier JM, Andrieu G, Peres D, Robin E, Kipnis E, et al. Gabapentin attenuates late but not early postoperative pain after thyroidectomy with superficial cervical plexus block. *Anesthesia and Analgesia* 2008;**107**(5):1720-5. [PMID: 18931238]

Burke 2010 *{published data only}*

Burke SM, Shorten GD. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. *Anesthesia and Analgesia* 2010;**110**(4):1180-5. [PMID: 20103545]

Buvanendran 2010 *{published data only}*

Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesthesia and Analgesia* 2010;**110**(1):199-207. [PMID: 19910619]

Chan 2011 *{published data only}*

Chan MT, Wan AC, Gin T, Leslie K, Myles PS. Chronic postsurgical pain after nitrous oxide anesthesia. *Pain* 2011;**152**(11):2514-20. [PMID: 21889262]

Chaparro 2010 *{published data only}*

* Chaparro LE, Munoz Y, Gallo CA, Alvarez HA, Restrepo SM, Perez N, Restrepo L. Pain and Sensory Symptoms Following Augmentation Mammoplasty: A Long Term Follow-Up Study with Intraoperative Ketamine Use [Dolor y síntomas sensoriales después de mamoplastia estética de aumento: un estudio de seguimiento a largo plazo posterior al uso intraoperatorio de ketamina]. *Revista Colombiana Anestesiologia* 2010;**38**(2):204-12.

Clarke 2009 *{published data only}*

Clarke H, Pereira S, Kennedy D, Andrion J, Mitsakakis N, Gollish J, et al. Adding gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty. *Acta Anaesthesiologica Scandinavica* 2009;**53**(8):1073-83. [PMID: 19572933]

Crousier 2008 *{published data only}*

Crousier M, Cognet V, Khaled M, Gueugniaud PY, Piriou V. Effect of ketamine on prevention of postmastectomy chronic pain. A pilot study [Effet de la ketamine dans la prevention des douleurs chroniques post-mastectomies. Etude pilote]. *Annales Francaises d'Anesthesie et de Reanimation* 2008;**27**(12):987-93. [PMID: 19027263]

De Kock 2001 *{published data only}*

De Kock M, Lavand'homme P, Waterloos H. 'Balanced analgesia' in the perioperative period: is there a place for ketamine? *Pain* 2001;**92**(3):373-80. [PMID: 11376910]

Duale 2009 *{published data only}*

Duale C, Sibaud F, Guastella V, Vallet L, Gimbert YA, Taheri H, et al. Perioperative ketamine does not prevent chronic pain after thoracotomy. *European Journal of Pain (London, England)* 2009;**13**(5):497-505. [PMID: 18783971]

Dullenkopf 2009 *{published data only}*

Dullenkopf A, Muller R, Dillmann F, Wiedemeier P, Hegi TR, Gautschi S. An intraoperative pre-incision single dose of intravenous ketamine does not have an effect on postoperative analgesic requirements under clinical conditions. *Anaesthesia and Intensive Care* 2009;**37**(5):753-7. [PMID: 19775039]

Eisenberg 2007 *{published data only}*

Eisenberg E, Pud D, Koltun L, Loven D. Effect of early administration of the N-methyl-d-aspartate receptor antagonist amantadine on the development of postmastectomy pain syndrome: a prospective pilot study. *The Journal of Pain* 2007;**8**(3):223-9. [PMID: 16996315]

Fassoulaki 2001 *{published data only}*

Fassoulaki A, Sarantopoulos C, Melemeni A, Hogan Q. Regional block and mexiletine: the effect on pain after cancer breast surgery. *Regional Anesthesia and Pain Medicine* 2001;**26**(3):223-8. [PMID: 11359221]

Fassoulaki 2002 *{published data only}*

Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesthesia and Analgesia* 2002;**95**(4):985-91, table of contents. [PMID: 12351281]

Fransen 2006 *{published data only}*

Fransen M, Anderson C, Douglas J, MacMahon S, Neal B, Norton R, et al. Safety and efficacy of routine postoperative ibuprofen for pain and disability related to ectopic bone formation after hip replacement surgery (HIPAID): randomised controlled trial. *BMJ (Clinical research ed.)* 2006;**333**(7567):519. [PMID: 16885182]

Gianesello 2012 *{published data only}*

Gianesello L, Pavoni V, Barboni E, Galeotti I, Nella A. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. *Journal of Neurosurgical Anesthesiology* 2012;**24**(2):121-6. [PMID: 22045156]

Grigoras 2012 *{published data only}*

Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast

surgery. *The Clinical Journal of Pain* 2012;**28**(7):567-72. [PMID: 22699129]

Hayes 2004 *{published data only}*

Hayes C, Armstrong-Brown A, Burstal R. Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: a randomized, controlled trial. *Anaesthesia and Intensive Care* 2004;**32**(3):330-8. [PMID: 15264726]

Ilkjaer 2000 *{published data only}*

Ilkjaer S, Bach LF, Nielsen PA, Wernberg M, Dahl JB. Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. *Pain* 2000;**86**(1-2):19-24. [PMID: 10779656]

Karanikolas 2011 *{published data only}*

Karanikolas M, Aretha D, Tsolakis I, Monantera G, Kiekkas P, Papadoulas S, et al. Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence, and frequency: a prospective, randomized, clinical trial. *Anesthesiology* 2011;**114**(5):1144-54. [PMID: 21368651]

Katz 2004a *{published data only}*

Katz J, Schmid R, Snijdelaar DG, Coderre TJ, McCartney CJ, Wowk A. Pre-emptive analgesia using intravenous fentanyl plus low-dose ketamine for radical prostatectomy under general anesthesia does not produce short-term or long-term reductions in pain or analgesic use. *Pain* 2004;**110**(3):707-18. [PMID: 15288412]

Kim 2010 *{published data only}*

Kim SY, Jeong JJ, Chung WY, Kim HJ, Nam KH, Shim YH. Perioperative administration of pregabalin for pain after robot-assisted endoscopic thyroidectomy: a randomized clinical trial. *Surgical Endoscopy* 2010;**24**(11):2776-81. [PMID: 20376496]

Kinney 2011 *{published data only}*

Kinney MA, Mantilla CB, Carns PE, Passe MA, Brown MJ, Hooten WM, et al. Preoperative gabapentin for acute post-thoracotomy analgesia: A randomized, double-blinded, active placebo-controlled study. *Pain Practice* 2011;**12**(3):175-83. [PMID: 21676165]

Lakdja 1997 *{published data only}*

Lakdja F, Dixmerias F, Bussieres E, Fonrouge JM, Lobera A. Preventive analgesic effect of intraoperative administration of ibuprofen-arginine on postmastectomy pain syndrome [Effet analgesique preventif d'une administration perioperatoire d'ibuprofene-arginine sur le syndrome douloureux postmastectomie]. *Bulletin du Cancer* 1997;**84**(3):259-63. [PMID: 9207871]

Malek 2006 *{published data only}*

* Malek J, Kurzova A, Bendova M, Noskova P, Strunova M, Vedral T. The prospective study on the effect of a preemptive long-term postoperative administration of a low-dose ketamine on the incidence of chronic post-mastectomy pain. [Efekt perioperacniho podavani ketaminu na potlaceni vzniku chronicke bolesti po operaci prsu - prospektivni studie]. *Anesteziologie a Intenzivni Medicina* 2006;**17**(1):34-37.

Moore 2011 *{published data only}*

Moore A, Costello J, Wieczorek P, Shah V, Taddio A, Carvalho JC. Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. *Anesthesia and Analgesia* 2011;**112**(1):167-73. [PMID: 21081764]

Nikolajsen 2006 *{published data only}*

Nikolajsen L, Finnerup NB, Kramp S, Vimtrup AS, Keller J, Jensen TS. A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology* 2006;**105**(5):1008-15. [PMID: 17065896]

Perrin 2009 *{published data only}*

Perrin SB, Purcell AN. Intraoperative ketamine may influence persistent pain following knee arthroplasty under combined general and spinal anaesthesia: a pilot study. *Anaesthesia and Intensive Care* 2009;**37**(2):248-53. [PMID: 19400488]

Pesonen 2011 *{published data only}*

Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P, et al. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. *British Journal of Anaesthesia* 2011;**106**(6):873-81. [PMID: 21474474]

Remerand 2009 *{published data only}*

Remerand F, Le Tendre C, Baud A, Couvret C, Pourrat X, Favard L, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesthesia and Analgesia* 2009;**109**(6):1963-71. [PMID: 19923527]

Romundstad 2006 *{published data only}*

Romundstad L, Breivik H, Roald H, Skolleborg K, Romundstad PR, Stubhaug A. Chronic pain and sensory changes after augmentation mammoplasty: long term effects of preincisional administration of methylprednisolone. *Pain* 2006;**124**(1-2):92-9. [PMID: 16650580]

Schley 2007 *{published data only}*

Schley M, Topfner S, Wiech K, Schaller HE, Konrad CJ, Schmelz M, et al. Continuous brachial plexus blockade in combination with the NMDA receptor antagonist memantine prevents phantom pain in acute traumatic upper limb amputees. *European Journal of Pain (London, England)* 2007;**11**(3):299-308. [PMID: 16716615]

Sen 2009 *{published data only}*

Sen H, Sizlan A, Yanarates O, Senol MG, Inangil G, Sucullu I, et al. The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy. *European Journal of Anaesthesiology* 2009;**26**(9):772-6. [PMID: 19424073]

Sen 2009a *{published data only}*

Sen H, Sizlan A, Yanarates O, Emirkadi H, Ozkan S, Dagli G, et al. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. *Anesthesia and Analgesia* 2009;**109**(5):1645-50. [PMID: 19843803]

Spreng 2010 *{published data only}*

Spreng AJ, Dahl V, Raeder J. Effects of perioperative S (+) ketamine infusion added to multimodal analgesia inpatients undergoing ambulatory haemorrhoidectomy. *Scandinavian Journal of Pain* 2010;**1**(2):100-5.

Suzuki 2006 *{published data only}*

Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimada Y, Sakamoto A. Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* 2006;**105**(1):111-9. [PMID: 16810002]

Sveticic 2008 *{published data only}*

Sveticic G, Farzanegan F, Zmoos P, Zmoos S, Eichenberger U, Curatolo M. Is the combination of morphine with ketamine better than morphine alone for postoperative intravenous patient-controlled analgesia? *Anesthesia and Analgesia* 2008;**106**(1):287-93, table of contents. [PMID: 18165592]

Ucak 2011 *{published data only}*

Ucak A, Onan B, Sen H, Selcuk I, Turan A, Yilmaz AT. The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 2011;**25**(5):824-9. [PMID: 21232979]

Weis 2006 *{published data only}*

Weis F, Kilger E, Roozendaal B, de Quervain DJ, Lamm P, Schmidt M, et al. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: a randomized study. *The Journal of Thoracic and Cardiovascular Surgery* 2006;**131**(2):277-82. [PMID: 16434254]

References to studies excluded from this review

Arcioni 2007 *{published data only}*

Arcioni R, Palmisani S, Tigano S, Santorsola C, Sauli V, Romano S, et al. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce post-operative analgesic requirements: a prospective, randomized, double-blind, controlled trial in patients undergoing major orthopedic surgery. *Acta Anaesthesiologica Scandinavica* 2007;**51**(4):482-9. [PMID: 17378788]

Bell 2001 *{published data only}*

Bell RF, Sivertsen A, Mowinkel P, Vindenes H. A bilateral clinical model for the study of acute and chronic pain after breast-reduction surgery. *Acta Anaesthesiologica Scandinavica* 2001;**45**(5):576-82. [PMID: 11309007]

Biyik 2009 *{published data only}*

Biyik I, Gulculer M, Karabiga M, Ergene O, Tayyar N. Efficacy of gabapentin versus diclofenac in the treatment of chest pain and paresthesia in patients with sternotomy. *Anadolu Kardiyoloji Dergisi* 2009;**9**(5):390-6. [PMID: 19819790]

Bone 2002 *{published data only}*

Bone M, Critchley P, Buggy DJ. Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. *Regional Anesthesia and Pain Medicine* 2002;**27**(5):481-6. [PMID: 12373695]

Buvanendran 2003 *{published data only}*

Buvanendran A, Kroin JS, Tuman KJ, Lubenow TR, Elmofty D, Moric M, et al. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial. *JAMA* 2003;**290**(18):2411-8. [PMID: 14612477]

Camilleri 2001 *{published data only}*

Camilleri M, Chey WY, Mayer EA, Northcutt AR, Heath A, Dukes GE, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Archives of Internal Medicine* 2001;**161**(14):1733-40. [PMID: 11485506]

Capdevila 1999 *{published data only}*

Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999;**91**(1):8-15. [PMID: 10422923]

Chiu 2008 *{published data only}*

Chiu KM, Wu CC, Wang MJ, Lu CW, Shieh JS, Lin TY, et al. Local infusion of bupivacaine combined with intravenous patient-controlled analgesia provides better pain relief than intravenous patient-controlled analgesia alone in patients undergoing minimally invasive cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2008;**135**(6):1348-52. [PMID: 18544384]

Clarke 2010 *{published data only}*

Clarke H, Kay J, Mitsakakis N, Katz J. Acute pain after total hip arthroplasty does not predict the development of chronic postsurgical pain 6 months later. *Journal of Anesthesia* 2010 Aug;**24**(4):537-43.

Cobellis 2004 *{published data only}*

Cobellis L, Razzi S, De Simone S, Sartini A, Fava A, Danero S, et al. The treatment with a COX-2 specific inhibitor is effective in the management of pain related to endometriosis. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2004;**116**(1):100-2. [PMID: 15294376]

Cohen 2006 *{published data only}*

Cohen SP, Sireci A, Wu CL, Larkin TM, Williams KA, Hurley RW. Pulsed radiofrequency of the dorsal root ganglia is superior to pharmacotherapy or pulsed radiofrequency of the intercostal nerves in the treatment of chronic postsurgical thoracic pain. *Pain Physician* 2006;**9**(3):227-35. [PMID: 16886031]

Elkaradawy 2012 *{published data only}*

Elkaradawy S, Nasr M, Elkerm Y, El Deeb M, Yassine O. The effect of multimodal balanced anaesthesia and long term gabapentin on neuropathic pain, nitric oxide and interleukin-1β following breast surgery. *Egyptian Journal of Anaesthesia* 2012;**28**(1):67-78.

Essving 2009 *{published data only}*

Essving P, Axelsson K, Kjellberg J, Wallgren O, Gupta A, Lundin A. Reduced hospital stay, morphine consumption, and pain intensity with local infiltration analgesia after unicompartmental knee arthroplasty. *Acta Orthopaedica* 2009;**80**(2):213-9. [PMID: 19404806]

Essving 2010 *{published data only}*

Essving P, Axelsson K, Kjellberg J, Wallgren O, Gupta A, Lundin A. Reduced morphine consumption and pain intensity with local infiltration analgesia (LIA) following total knee arthroplasty. *Acta Orthopaedica* 2010;**81**(3):354-60. [PMID: 20450425]

Fassoulaki 2000 *{published data only}*

Fassoulaki A, Sarantopoulos C, Melemeni A, Hogan Q. EMLA reduces acute and chronic pain after breast surgery for cancer. *Regional Anesthesia and Pain Medicine* 2000;**25**(4):350-5. [PMID: 10925929]

Fassoulaki 2005 *{published data only}*

Fassoulaki A, Triga A, Melemeni A, Sarantopoulos C. Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. *Anesthesia and Analgesia* 2005;**101**(5):1427-32. [PMID: 16244006]

Fassoulaki 2006 *{published data only}*

Fassoulaki A, Stamatakis E, Petropoulos G, Siafaka I, Hassiakos D, Sarantopoulos C. Gabapentin attenuates late but not acute pain after abdominal hysterectomy. *European Journal of Anaesthesiology* 2006;**23**(2):136-41. [PMID: 16426468]

Fassoulaki 2007 *{published data only}*

Fassoulaki A, Melemeni A, Stamatakis E, Petropoulos G, Sarantopoulos C. A combination of gabapentin and local anaesthetics attenuates acute and late pain after abdominal hysterectomy. *European Journal of Anaesthesiology* 2007;**24**(6):521-8. [PMID: 17207299]

Fransen 2004 *{published data only}*

Fransen M. Preventing chronic ectopic bone-related pain and disability after hip replacement surgery with perioperative ibuprofen. A multicenter, randomized, double-blind, placebo-controlled trial (HIPAID). *Controlled Clinical Trials* 2004;**25**(2):223-33. [PMID: 15020038]

Guan 2005 *{published data only}*

Guan ZP, Feng Y, Lu HS. Effect of perioperative use of selective cyclooxygenase-2 inhibitor on postoperative pain, bleeding volume and functional recovery of the knee joints after joint replacement of both knees. [圍手術期使用選擇性環氧合酶2抑制劑對雙膝關節置換術后疼痛、出血量以及膝關節功能恢復的影響] . *Chinese Journal of Clinical Rehabilitation* 2005;**9**(6):4-7.

Gupta 2006 *{published data only}*

Gupta A, Fant F, Axelsson K, Sandblom D, Rykowski J, Johansson JE, et al. Postoperative analgesia after radical retropubic prostatectomy: a double-blind comparison between low thoracic epidural and patient-controlled intravenous analgesia. *Anesthesiology* 2006;**105**(4):784-93. [PMID: 17006078]

Harding 1991 *{published data only}*

Harding SP, Porter SM. Oral acyclovir in herpes zoster ophthalmicus. *Current Eye Research* 1991;**10 Suppl**:177-82. [PMID: 1864092]

Hartrick 2011 *{published data only}*

Hartrick CT, Pestano C, Carlson N, Hartrick S. Capsaicin instillation for postoperative pain following total knee arthroplasty: a preliminary report of a randomized, double-blind, parallel-group, placebo-controlled, multicentre trial. *Clinical Drug Investigation* 2011;**31**(12):877-82. [PMID: 21971213]

Honigmann 2007 *{published data only}*

Honigmann P, Fischer H, Kurmann A, Audige L, Schupfer G, Metzger J. Investigating the effect of intra-operative infiltration with local anaesthesia on the development of chronic postoperative pain after inguinal hernia repair. A randomized placebo controlled triple blinded and group sequential study design [NCT00484731]. *BMC Surgery* 2007;**7**:22. [PMID: 17986324]

Huse 2001 *{published data only}*

Huse E, Larbig W, Flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 2001;**90**(1-2):47-55. [PMID: 11166969]

Jaeger 1992 *{published data only}*

Jaeger H, Maier C. Calcitonin in phantom limb pain: a double-blind study. *Pain* 1992;**48**(1):21-7.

Jirarattanaphochai 2007 *{published data only}*

Jirarattanaphochai K, Jung S, Thienthong S, Krisanaprakornkit W, Sumananont C. Peridural methylprednisolone and wound infiltration with bupivacaine for postoperative pain control after posterior lumbar spine surgery: a randomized double-blinded placebo-controlled trial. *Spine* 2007;**32**(6):609-16; discussion 617. [PMID: 17413463]

Kadic 2009 *{published data only}*

Kadic L, Boonstra MC, De Waal Malefijt MC, Lako SJ, Van Egmond J, Driessen JJ. Continuous femoral nerve block after total knee arthroplasty? *Acta Anaesthesiologica Scandinavica* 2009;**53**(7):914-20. [PMID: 19388886]

Kamencic 2008 *{published data only}*

Kamencic H, Thiel JA. Pentoxifylline after conservative surgery for endometriosis: a randomized, controlled trial. *Journal of Minimally Invasive Gynecology* 2008;**15**(1):62-6. [PMID: 18262146]

Kampe 2003 *{published data only}*

Kampe S, Kiencke P, Delis A, Auweiler M, Konig DP, Kasper SM. The continuous epidural infusion of ropivacaine 0.1% with 0.5 microg x mL(-1) sufentanil provides effective postoperative analgesia after total hip replacement: a pilot study. *Canadian Journal of Anaesthesia = Journal Canadien d'Anesthesie* 2003;**50**(6):580-5. [PMID: 12826550]

Katz 2004 *{published data only}*

Katz J, Cohen L. Preventive analgesia is associated with reduced pain disability 3 weeks but not 6 months after

major gynecologic surgery by laparotomy. *Anesthesiology* 2004;**101**(1):169-74. [PMID: 15220787]

Kim 2011 *{published data only}*

Kim SY, Song JW, Park B, Park S, An YJ, Shim YH. Pregabalin reduces post-operative pain after mastectomy: a double-blind, randomized, placebo-controlled study. *Acta Anaesthesiologica Scandinavica* 2011;**55**(3):290-6. [PMID: 21288209]

Kollender 2008 *{published data only}*

Kollender Y, Bickels J, Stocki D, Maruoani N, Chazan S, Nirkin A, et al. Subanaesthetic ketamine spares postoperative morphine and controls pain better than standard morphine does alone in orthopaedic-oncological patients. *European Journal of Cancer (Oxford, England)* 2008;**44**(7):954-62. [PMID: 18396035]

Koninckx 2008 *{published data only}*

Koninckx PR, Craessaerts M, Timmerman D, Cornillie F, Kennedy S. Anti-TNF-alpha treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial. *Human Reproduction (Oxford, England)* 2008;**23**(9):2017-23. [PMID: 18556683]

Lambert 2001 *{published data only}*

Lambert AW, Dashfield AK, Cosgrove C, Wilkins DC, Walker AJ, Ashley S. Randomized prospective study comparing preoperative epidural and intraoperative perineural analgesia for the prevention of postoperative stump and phantom limb pain following major amputation. *Regional Anesthesia and Pain Medicine* 2001;**26**(4):316-21. [PMID: 11464349]

Lampl 2002 *{published data only}*

Lampl C, Yazdi K, Roper C. Amitriptyline in the prophylaxis of central poststroke pain. Preliminary results of 39 patients in a placebo-controlled, long-term study. *Stroke* 2002;**33**(12):3030-2. [PMID: 12468808]

Lavand'homme 2005 *{published data only}*

Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. *Anesthesiology* 2005;**103**(4):813-20. [PMID: 16192774]

Lynch 2003 *{published data only}*

Lynch ME, Clark AJ, Sawynok J. Intravenous adenosine alleviates neuropathic pain: a double blind placebo controlled crossover trial using an enriched enrolment design. *Pain* 2003;**103**(1-2):111-7. [PMID: 12749965]

Maier 2003 *{published data only}*

Maier C, Dertwinkel R, Mansourian N, Hosbach I, Schwenkreis P, Senne I, et al. Efficacy of the NMDA-receptor antagonist memantine in patients with chronic phantom limb pain--results of a randomized double-blinded, placebo-controlled trial. *Pain* 2003;**103**(3):277-83. [PMID: 12791434]

Martin 2008 *{published data only}*

Martin F, Martinez V, Mazoit JX, Bouhassira D, Cherif K, Gentili ME, et al. Antiinflammatory effect of peripheral nerve blocks after knee surgery: clinical and biologic evaluation. *Anesthesiology* 2008;**109**(3):484-90. [PMID: 18719447]

Morin 2005 *{published data only}*

Morin AM, Kratz CD, Eberhart LH, Dinges G, Heider E, Schwarz N, et al. Postoperative analgesia and functional recovery after total-knee replacement: comparison of a continuous posterior lumbar plexus (psoas compartment) block, a continuous femoral nerve block, and the combination of a continuous femoral and sciatic nerve block. *Regional Anesthesia and Pain Medicine* 2005;**30**(5):434-45. [PMID: 16135347]

Nehler 2007 *{published data only}*

Nehler MR, Brass EP, Anthony R, Dormandy J, Jiao J, McNamara TO, et al. Adjunctive parenteral therapy with lipo-ecraprost, a prostaglandin E1 analog, in patients with critical limb ischemia undergoing distal revascularization does not improve 6-month outcomes. *Journal of Vascular Surgery* 2007;**45**(5):953-60; discussion 960-1. [PMID: 17350216]

Nesher 2008 *{published data only}*

Nesher N, Serovian I, Marouani N, Chazan S, Weinbroum AA. Ketamine spares morphine consumption after transthoracic lung and heart surgery without adverse hemodynamic effects. *Pharmacological Research* 2008;**58**(1):38-44. [PMID: 18602474]

Nesher 2009 *{published data only}*

Nesher N, Ekstein MP, Paz Y, Marouani N, Chazan S, Weinbroum AA. Morphine with adjuvant ketamine vs higher dose of morphine alone for immediate postthoracotomy analgesia. *Chest* 2009;**136**(1):245-52. [PMID: 18753471]

Nikolajsen 1997 *{published data only}*

Nikolajsen L, Ilkjaer S, Christensen JH, Kroner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. *Lancet* 1997;**350**(9088):1353-7. [PMID: 9365449]

Nikolajsen 2000 *{published data only}*

Nikolajsen L, Gottrup H, Kristensen AG, Jensen TS. Memantine (a N-methyl-D-aspartate receptor antagonist) in the treatment of neuropathic pain after amputation or surgery: a randomized, double-blinded, cross-over study. *Anesthesia and Analgesia* 2000;**91**(4):960-6. [PMID: 11004057]

Nissman 2008 *{published data only}*

Nissman SA, Tractenberg RE, Babbar-Goel A, Pasternak JF. Oral gabapentin for the treatment of postoperative pain after photorefractive keratectomy. *American Journal of Ophthalmology* 2008;**145**(4):623-9. [PMID: 18226799]

Obata 1999 *{published data only}*

Obata H, Saito S, Fujita N, Fuse Y, Ishizaki K, Goto F. Epidural block with mepivacaine before surgery reduces long-term post-thoracotomy pain. *Canadian Journal of Anaesthesia = Journal Canadien d'Anesthesie* 1999;**46**(12):1127-32. [PMID: 10608205]

Parker 2006 *{published data only}*

Parker JD, Leondires M, Sinaii N, Premkumar A, Nieman LK, Stratton P. Persistence of dysmenorrhea and nonmenstrual pain after optimal endometriosis surgery may indicate adenomyosis. *Fertility and Sterility* 2006;**86**(3):711-5. [PMID: 16782099]

Perniola 2009 *{published data only}*

Perniola A, Gupta A, Crafoord K, Darvish B, Magnuson A, Axelsson K. Intraabdominal local anaesthetics for postoperative pain relief following abdominal hysterectomy: a randomized, double-blind, dose-finding study. *European Journal of Anaesthesiology* 2009;**26**(5):421-9. [PMID: 19521298]

Reuben 2004 *{published data only}*

Reuben SS, Makari-Judson G, Lurie SD. Evaluation of efficacy of the perioperative administration of venlafaxine XR in the prevention of postmastectomy pain syndrome. *Journal of Pain and Symptom Management* 2004;**27**(2):133-9. [PMID: 15157037]

Reuben 2005 *{published data only}*

Reuben S, Gutta SB, Maciolek H, Sklar J, Redford J. Effect of initiating a preventative multimodal analgesic regimen upon long-term patient outcomes after anterior cruciate ligament reconstruction for same-day surgery: A 1200-patient case series. *Acute Pain* 2005;**7**:65-73.

Reuben 2006 *{published data only}*

Reuben SS, Ekman EF, Raghunathan K, Steinberg RB, Blinder JL, Adesioye J. The effect of cyclooxygenase-2 inhibition on acute and chronic donor-site pain after spinal-fusion surgery. *Regional Anesthesia and Pain Medicine* 2006;**31**(1):6-13. [PMID: 16418018]

Reuben 2007 *{published data only}*

Reuben SS, Ekman EF. The effect of initiating a preventive multimodal analgesic regimen on long-term patient outcomes for outpatient anterior cruciate ligament reconstruction surgery. *Anesthesia and Analgesia* 2007;**105**(1):228-32. [PMID: 17578979]

Reuben 2008 *{published data only}*

Reuben SS, Buvenandran A, Katz B, Kroin JS. A prospective randomized trial on the role of perioperative celecoxib administration for total knee arthroplasty: improving clinical outcomes. *Anesthesia and Analgesia* 2008;**106**(4):1258-64, table of contents. [PMID: 18349203]

Rhodes 1988 *{published data only}*

Rhodes M, Lennard TW, Farndon JR, Taylor RM. Cholecystokinin (CCK) provocation test: long-term follow-up after cholecystectomy. *The British Journal of Surgery* 1988;**75**(10):951-3. [PMID: 3146403]

Ryu 2011 *{published data only}*

Ryu HG, Lee CJ, Kim YT, Bahk JH. Preemptive low-dose epidural ketamine for preventing chronic postthoracotomy pain: a prospective, double-blinded, randomized, clinical trial. *The Clinical Journal of Pain* 2011;**27**(4):304-8. [PMID: 21178605]

Salengros 2010 *{published data only}*

Salengros JC, Huybrechts I, Ducart A, Faraoni D, Marsala C, Barvais L, et al. Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *Journal of Cardiothoracic and Vascular Anesthesia* 2010;**24**(4):608-16. [PMID: 20005744]

Sanders 2009 *{published data only}*

Sanders JC, Gerstein N, Torgeson E, Abram S. Intrathecal baclofen for postoperative analgesia after total knee arthroplasty. *Journal of Clinical Anesthesia* 2009;**21**(7):486-92. [PMID: 20006256]

Senturk 2002 *{published data only}*

Senturk M, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalcin S, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesthesia and Analgesia* 2002;**94**(1):11-5, table of contents. [PMID: 11772793]

Sesti 2007 *{published data only}*

Sesti F, Pietropolli A, Capozzolo T, Broccoli P, Pierangeli S, Bollea MR, et al. Hormonal suppression treatment or dietary therapy versus placebo in the control of painful symptoms after conservative surgery for endometriosis stage III-IV. A randomized comparative trial. *Fertility and Sterility* 2007;**88**(6):1541-7. [PMID: 17434511]

Singh 2007 *{published data only}*

Singh K, Phillips FM, Kuo E, Campbell M. A prospective, randomized, double-blind study of the efficacy of postoperative continuous local anesthetic infusion at the iliac crest bone graft site after posterior spinal arthrodesis: a minimum of 4-year follow-up. *Spine* 2007;**32**(25):2790-6. [PMID: 18245999]

Solak 2007 *{published data only}*

Solak O, Metin M, Esme H, Solak O, Yaman M, Pekcolaklar A, et al. Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain. *European Journal of Cardio-Thoracic Surgery* 2007;**32**(1):9-12. [PMID: 17442584]

Tramer 1996 *{published data only}*

Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. *Anesthesiology* 1996;**84**(2):340-7. [PMID: 8602664]

Wai 2010 *{published data only}*

Wai EK, Sathiaseelan S, O'Neil J, Simchison BL. Local administration of morphine for analgesia after autogenous anterior or posterior iliac crest bone graft harvest for spinal fusion: a prospective, randomized, double-blind, placebo-controlled study. *Anesthesia and Analgesia* 2010;**110**(3):928-33. [PMID: 20042446]

Waikakul 1999 *{published data only}*

Waikakul S, Unnanantana A, Vanadurongwan V. The role of allopurinol in digital replantation. *Journal of Hand Surgery (Edinburgh, Scotland)* 1999;**24**(3):325-7. [PMID: 10433447]

White 2007 *{published data only}*

White PF, Sacan O, Tufanogullari B, Eng M, Nuangchamnong N, Ogunnaike B. Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. *Canadian Journal of Anaesthesia = Journal Canadien d'Anesthesie* 2007;**54**(5):342-8. [PMID: 17470884]

Wu 2008 *{published data only}*

Wu CL, Agarwal S, Tella PK, Klick B, Clark MR, Haythornthwaite JA, et al. Morphine versus mexiletine for

treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology* 2008;**109**(2):289-96. [PMID: 18648238]

References to studies awaiting assessment

Bilgen 2012 *{published data only}*

Bilgen S, Köner O, Türe H, Menda F, Fiçicioğlu C, Aykaç B. Effect of three different doses of ketamine prior to general anaesthesia on postoperative pain following Caesarean delivery: a prospective randomized study.. *Minerva Anesthesiology* 2012 Apr;**78**(4):442-9.

Cohen 2013 *{published data only}*

Cohen SP, Galvagno SM, Plunkett A, Harris D, Kurihara C, Turabi A, Rehrig S, Buckenmaier CC 3rd, Chelly JE. A multicenter, randomized, controlled study evaluating preventive etanercept on postoperative pain after inguinal hernia repair.. *Anesthesia and Analgesia* 2013 Feb;**116**(2):455-62.

Fassoulaki 2012 *{published data only}*

Fassoulaki A, Melemeni A, Tsaroucha A, Paraskeva A. Perioperative pregabalin for acute and chronic pain after abdominal hysterectomy or myomectomy: a randomised controlled trial.. *European Journal of Anaesthesiology* 2012 Nov;**29**(11):531-6.

Martinez 2013 *{published data only}*

Martinez V, Szekely B, Lemarié J, Martin F, Gentili M, Ben Ammar S, Lepeintre JF, Garreau de Loubresse C, Chauvin M, Bouhassira D, Fletcher D. The efficacy of a glial inhibitor, minocycline, for preventing persistent pain after lumbar discectomy: A randomized, double-blind, controlled study.. *Pain.* 2013 Aug;**154**(8):1197-203.

Mendola 2012 *{published data only}*

Mendola C, Cammarota G, Netto R, Cecci G, Pisterna A, Ferrante D, Casadio C, Della Corte F. S+ -ketamine for control of perioperative pain and prevention of post thoracotomy pain syndrome: a randomized, double-blind study.. *Minerva Anesthesiology* 2012 Jul;**78**(7):757-66.

NCT00224588 *{unpublished data only}*

Short 2012 *{published data only}*

Short J, Downey K, Bernstein P, Shah V, Carvalho JC. A single preoperative dose of gabapentin does not improve postcesarean delivery pain management: a randomized, double-blind, placebo-controlled dose-finding trial.. *Anesthesia and Analgesia* 2012 Dec;**115**(6):1336-42.

References to ongoing studies

NCT00129597 *{unpublished data only}*

Effect of Ketalar to Prevent Postoperative Chronic Pain After Mastectomy. Ongoing study. December 2004. Contact author for more information.

NCT00442546 *{unpublished data only}*

Efficacy And Safety Of Pregabalin For Pain Following Total Knee Replacement. Ongoing study. May 2007. Contact author for more information.

NCT00468845 *{unpublished data only}*

Study Of The Efficacy And Safety Of Pregabalin Compared To Placebo For Treatment Of Post-Surgical Pain From Hysterectomy. Ongoing study. June 2007. Contact author for more information.

NCT00551135 *{unpublished data only}*

Surgical Pain After Inguinal Hernia Repair (SPAIHR). Ongoing study. January 2008. Contact author for more information.

NCT00583869 *{unpublished data only}*

Role of Pregabalin in Treatment of Post-Op Pain in Fracture Patients (LYRICA). Ongoing study. May 2007. Contact author for more information.

NCT00618423 *{unpublished data only}*

The Effect of Perioperative Ketamine on Acute and Chronic Pain After Major Back Surgery (KetaDol). Ongoing study. October 2007. Contact author for more information.

NCT00631891 *{unpublished data only}*

Pregabalin in Treating Pain in Women Undergoing Mastectomy or Lumpectomy. Ongoing study. December 2006. Contact author for more information.

NCT00663962 *{unpublished data only}*

Pregabalin and Post-thoracotomy Pain. Ongoing study. April 2008. Contact author for more information.

NCT00762099 *{unpublished data only}*

Perioperative Pregabalin Use, Rehabilitation, Pain Outcomes and Anxiety Following Hip Surgery (RCT). Ongoing study. May 2009. Contact author for more information.

NCT00852683 *{unpublished data only}*

The Effects of Peri-Operative Pregabalin on Post-Operative Pain Following Breast Cancer Surgery With Axillary Node Dissection: A Pilot Study. Ongoing study. May 2008. Contact author for more information.

NCT00905437 *{unpublished data only}*

Study To Investigate The Effectiveness Of Pregabalin For Management Of Patients Undergoing Total Hip Replacement. Ongoing study. November 2009. Contact author for more information.

NCT00967135 *{unpublished data only}*

Efficacy of Perioperative Pregabalin in Reducing the Incidence of Chronic Neuropathic Pain and Postthoracotomy Syndrome.. Ongoing study. June 2010. Contact author for more information.

NCT01022840 *{unpublished data only}*

The Preemptive Analgetic Potency of Low Dose S-Ketamine (Miniket). Ongoing study. February 2009. Contact author for more information.

NCT01116583 *{unpublished data only}*

The Effect of Gabapentin on Thoracic Epidural Analgesia Following Thoracotomy (GABATEA). Ongoing study. May 2011. Contact author for more information.

NCT01204242 *{unpublished data only}*

IV Lidocaine for Patients Undergoing Primary Breast Cancer Surgery: Effects on Postoperative Recovery and Cancer. Ongoing study. August 2009. Contact author for more information.

NCT01243801 *{unpublished data only}*

Prevention of Persistent Postsurgical Pain After Thoracotomy. Ongoing study. September 2008. Contact author for more information.

NCT01296347 *{unpublished data only}*

Low Dose Peri-operative IV Ketamine for Chronic Post-surgery Pain Prevention. Ongoing study. April 2011. Contact author for more information.

NCT01359059 *{unpublished data only}*

Pre- Versus Post-incisional Pregabalin for Postoperative Pain Attenuation and Analgesics Spare in Orthopedic Oncologic Patients. Ongoing study. June 2011. Contact author for more information.

NCT01391858 *{unpublished data only}*

Postoperative Pain and Morphine Consumption After Mastectomy - Lyrica. Ongoing study. December 2006. Contact author for more information.

NCT01480765 *{unpublished data only}*

Preventing Pain After Heart Surgery. Ongoing study. November 2011. Contact author for more information.

Additional references

Andreae 2008

Andreae MH, Andreae DA, Motschall E, Rücker G, Timmer A. Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No: CD007105. [DOI: 10.1002/14651858.CD007105]

Bhandari 2005

Bhandari M, Haynes RB. How to appraise the effectiveness of treatment. *World Journal of Surgery* 2005;**29**(5):570-5. [PMID: 15827841]

Burton 1999

Burton AW, Lee DH, Saab C, Chung JM. Preemptive intrathecal ketamine injection produces a long-lasting decrease in neuropathic pain behaviors in a rat model. *Regional Anesthesia and Acute Pain Management* 1999;**24**(3):208-13.

Cesena 1999

Cesena RM, Calcutt NA. Gabapentin prevents hyperalgesia during the formalin test in diabetic rats. *Neuroscience Letters* 1999;**262**(2):101-4.

Clarke 2012

Clarke H, Bonin RP, Orser BA, Englesakis M, Wijeysundera DN, Katz J. The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. *Anesthesia and analgesia* 2012;**115**(2):428-42. [PMID: 22415535]

Crombie 1998

Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. *Pain* 1998;**76**(1-2):167-71.

D'Mello 2008

D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. *British Journal of Anaesthesia* 2008;**101**(1):8-16.

Dahl 2011

Dahl JB, Kehlet H. Preventive analgesia. *Current Opinion in Anaesthesiology* 2011;**24**(3):331-8. [PMID: 21478742]

Dworkin 2005

Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;**113**(1-2):9-19. [PMID: 15621359]

Dworkin 2010

Dworkin RH, McDermott MP, Raja SN. Preventing chronic postsurgical pain: how much of a difference makes a difference? Anesthesiology 2010;**112**(3):516-8. [PMID: 20124976]

Higgins 2011

Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed.)* 2011;**343**:d5928. [PMID: 22008217]

Katz 2009

Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Review of Neurotherapeutics* 2009;**9**(5):723-44. [PMID: 19402781]

Kehlet 2006

Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;**367**(9522):1618-25.

Kehlet 2010

Kehlet H, Rathmell JP. Persistent postsurgical pain: the path forward through better design of clinical studies. Anesthesiology 2010;**112**(3):514-5. [PMID: 20124977]

McCarson 2005

McCarson KE, Ralya A, Reisman SA, Enna SJ. Amitriptyline prevents thermal hyperalgesia and modifications in rat spinal cord GABA(B) receptor expression and function in an animal model of neuropathic pain. *Biochemical Pharmacology* 2005;**71**(1-2):196-202.

Moore 1998

Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything--large amounts of information are needed

to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**(3):209-16. [PMID: 9870574]

Nuesch 2010

Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, Egger M, Jüni P. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study.. *BMJ* 2010 Jul 16;**341. PubMed PMID: 20639294; PubMed Central PMCID: PMC2905513.**(c3515):doi: 10.1136/bmj.c3515.

Perkins 2000

Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* 2000;**93**:1123-33.

Rappaport 2010

Rappaport BA, Cerny I, Sanhai WR. ACTION on the prevention of chronic pain after surgery: public-private partnerships, the future of analgesic drug development. Anesthesiology 2010;**112**(3):509-10. [PMID: 20124974]

Wen 2007

Wen YR, Suter MR, Kawasaki Y, Huang J, Pertin M, Kohno T, et al. Nerve conduction blockade in the sciatic nerve prevents but does not reverse the activation of p38 mitogen-activated protein kinase in spinal microglia in the rat spared nerve injury model. *Anesthesiology* 2007;**107**(2):312-21.

Woolf 1991

Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991;**44**(3):293-9.

Woolf 2000

Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science* 2000;**288**(5472):1765-9.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Amr 2010

Study characteristics	
Methods	Single center, randomized, double blind, 3 arms, placebo-controlled trial for 6 months
Participants	150 patients scheduled for either partial or radical mastectomy with axillary dissection
Interventions	In the (Group 1) venlafaxine group, patients received 37.5 mg of venlafaxine extended release along with another capsule (identical in appearance to the gabapentin capsules) once daily at bed time. Patients in the (Group 2) gabapentin group received 300 mg of gabapentin and another capsule (identical in appearance to the venlafaxine extended release capsules) once daily at bed time. Patients in the (Group 3) placebo group received 2 capsules that were filled with thin sugar (1 identical in appearance to the gabapentin capsules and the other identical to venlafaxine extended release capsules) once daily at bed time. Administration of the drugs started the evening before surgery and continued for the first 10 postoperative days, including the day of the surgery.
Outcomes	Pain scores at rest and movement-induced, morphine consumption, and side effects profile
Notes	Co-analgesia: morphine the first 24 hours; acetaminophen + codeine during the rest of the follow-up

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Shuffling envelopes: "A prospective, randomized (sealed envelopes indicate the group of assignment)...
Allocation concealment (selection bias)	Low risk	"An independent anesthesiologist, who did not participate in the study or data collection, read the number contained in the envelope and made group assignments".
Blinding of participants and personnel (performance bias)	Low risk	"Control (sugar filled) and/or treatment capsules for each group were packaged in group-specific bottles and coded as Bottle 1, Bottle 2, and Bottle 3 for Groups 1, 2, and 3, respectively. Yellow hard gelatin capsules (identical in

Amr 2010 *(Continued)*

All outcomes		appearance to the gabapentin capsules) and gray/peach capsules (identical in appearance to the venlafaxine extended release capsules) were filled with thin sugar. Envelopes, bottles with capsules, and coding were prepared by the pharmacy of the hospital.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind design was used, with both patients and postoperative assessors blinded to management protocol"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors reported no missing outcome data
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Low risk	No other potential sources of bias were detected

Bergeron 2009

Study characteristics		
Methods	Single center, randomized, double blind, placebo-controlled trial with long-term follow-up for 6 weeks and one year	
Participants	18 years or older patients undergoing elective primary total hip arthroplasty using spinal anesthesia to receive either dexamethasone (40 mg intravenous, n = 25) or saline placebo (n = 25)	
Interventions	A research collaborator,who did not participate in data collection, prepared an IV infusion bag containing 40 mg of dexamethasone or an equal volume of saline diluted into 40 mL of normal saline according to group allocation. Dexamethasone is colorless and causes no pain when given intravenously.	
Outcomes	Pain Scores, Harris Hip Score	
Notes	Morphine PCA, acetaminophen and Ibuprofen	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A research collaborator, who did not participate in data collection, prepared an IV infusion bag containing 40 mg of dexamethasone or an equal volume of saline diluted into 40 mL of normal saline according to group allocation. Dexamethasone is colorless and causes no pain when given intravenously".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The patients, anesthesiologists, nurses, and research coordinators gathering the data were blinded to the study arms".

Bergeron 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"We lost 10 patients to follow-up for nonmedical reasons due to a large referral network outside our province where patients are routinely followed radiographically and by phone interview".
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment
Other bias	Unclear risk	Fewer than 50 patients per arm

Brogly 2008

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 6 months
Participants	50 patients aged 18-75 yr, ASA I-III, undergoing scheduled total or partial thyroidectomy without lymph node dissection
Interventions	Gabapentin 1200 mg PO 2 hours before surgery or matching placebos (placebos are not described)
Outcomes	Primary outcome: analgesic drug consumption was assessed during the procedure and postoperatively in the postanesthesia care unit and after discharge to the ward. Over the first 24 h, pain levels at rest and during swallowing were measured. The day before operation and 6 mo after patients were asked to answer a neuropathic pain diagnostic questionnaire (DN2).
Notes	Coanalgesia: Superficial cervical plexus block for all participants. analgesic rescue: paracetamol + tramadol 50 mg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed by subgroups of 10 patients with a randomization table".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data (3/50) was minimum
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment
Other bias	High risk	Fewer than 50 patients per arm

Burke 2010

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 3 months
Participants	40 ASA physical status I and II patients, aged 18 - 60, with chronic lumbar sacral radiculopathy undergoing elective lumbar discectomy
Interventions	Pregabalin 300 mg 2h preoperatively + 150 mg POP at 12 h + 150 mg at 24h
Outcomes	Primary outcome was the change in the present pain intensity (PPI) (visual analog scale [VAS], 0–100 mm [PPI-VAS, McGill Pain Questionnaire]) from preoperatively to 3 months postoperatively
Notes	Intraop: paracetamol, morphine, NSAID and SC infiltration of bupivacaine. POP: codeine, acetaminophen and diclofenac

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"In this double-blind study, patients received pregabalin or placebo (sucrose) according to random allocation"
Allocation concealment (selection bias)	Low risk	"The medication was prescribed according to instructions in a sealed, opaque envelope by an anesthesiologist with no further involvement in the study".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"At 3 months postoperatively, patients once again completed the same 6 questionnaires in the presence of the same investigator".
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients dropped out from the study, only
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Buvanendran 2010

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 6 months
Participants	228 patients scheduled to undergo a primary total knee arthroplasty with a diagnosis of osteoarthritis of the operative knee and had the ability to understand and read English

Buvanendran 2010 *(Continued)*

Interventions	Patients randomized to the experimental arm of the study received pregabalin 300 mg orally (per os [PO]), 1–2 h before surgery, 150 mg twice daily for the first 10 postoperative days, 75 mg twice daily on Days 11 and 12, and 50 mg twice daily on Days 13 and 14
Outcomes	Adverse events related with the medication, Leeds Assessment of Neuropathic Symptoms and Signs pain scale, knee injury and Osteoarthritis Outcome Score–Physical function Short-form, Range of motion, epidural drug use and postoperative pain assessment
Notes	Co-analgesia: epidural Infusion of bupivacaine and fentanyl (PCEA)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized to a treatment group using a computer-generated randomization sequence".
Allocation concealment (selection bias)	Low risk	"During the study, only the dispensing pharmacist had knowledge of the study codes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Control patients received PO-matched placebo tablets, at identical time points, with both pregabalin and placebo capsules provided by Pfizer"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The personnel involved with postoperative pain assessments and management of the epidural infusion, physical therapists, and the study patients were blinded to group assignment".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups
Selective reporting (reporting bias)	High risk	Outcomes reported are clinically meaningful and validated. However, we detected some discrepancies in the definition of primary and secondary outcome between the published protocol (NCT00558753) and the publication.
Other bias	Low risk	No other potential sources of bias were detected

Chan 2011

Study characteristics

Methods	Multicenter, randomized, double-blind, controlled trial with long-term follow-up for at least three months
Participants	640 patients that were 18 yr or older scheduled, under general anesthesia, for surgery that included a skin incision and that was anticipated to exceed 2 hours, and were expected to be in the hospital for at least 3 days after surgery
Interventions	Intraoperative 70% nitrous oxide
Outcomes	The primary outcome of this follow-up study was chronic postsurgical pain according to the definition by the International Association for the Study of Pain. Secondary outcomes were the impact of chronic postsurgical pain on daily living.

Chan 2011 *(Continued)*

Notes	This study had a very high mortality rate at follow-up (34%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"….using a computer-generated code, accessed via an automated telephone voice recognition service".
Allocation concealment (selection bias)	Low risk	"…..automated telephone voice recognition service. Treatment assignment was stratified by site and elective/emergency status of the surgery, using permuted blocks".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Attending anesthesiologists were required to have knowledge of group identity for the safe administration of anesthesia, but group identity was concealed from the surgeon using drapes or cardboard to screen the anesthesia machine".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"At the end of the procedure, the intraoperative case report form and documentation of group identity were faxed to the data management center and then placed in an opaque envelope by the anesthesiologist. The envelope was then sealed to ensure blinding of research staff conducting the postoperative follow-ups".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This secondary analysis included the Hong Kong population only
Selective reporting (reporting bias)	Low risk	Outcomes reported for this secondary analysis are clinically meaningful and validated
Other bias	High risk	"Pain intensity was not described as an outcome in the original 2007 report".

Chaparro 2010

Study characteristics

Methods	Single center, randomized, double-blind, placebo-controlled trial with long-term follow-up for one year
Participants	106 patients scheduled to Esthetic Augmentation Mammaplasty were followed one year after the surgery
Interventions	Ketamine 25 IV before the beginning of the surgery plus additional 50 mg mixed with the IV anesthetic (2 mg of remifentanil)
Outcomes	Pain Scores, opioid consumption and adverse effects profile
Notes	Coanalgesia: Dipyrone and meperidine. Acetaminophen+Codeine and NSAIDs after discharge

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Throwing coin

Chaparro 2010 *(Continued)*

Allocation concealment (selection bias)	High risk	Randomization and allocation in groups of 4 patients. Two patients in a row receiving one treatment will predict the treatment for the next 2
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A registered nurse prepared the bags of saline and ketamine. She did not participated of the outcomes assessment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors were not aware of the treatment that the patients received
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant missing outcome data: 53%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Low risk	No other potential sources of bias were detected

Clarke 2009

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 6 months
Participants	126 Patients 18-75, ASA I, II or III undergoing total hip arthroplasty were eligible
Interventions	Patients were randomly assigned to one of 3 treatment groups (G1: Placebo/Placebo; G2: GBP/Placebo; and G3: Placebo/ GBP). Group 2 received gabapentin 600mg p.o. 2 h before surgery; the other groups received an identical-looking placebo capsule. Upon arrival to the recovery room, group 3 received gabapentin 600mg p.o.; the other groups received an identical-looking placebo capsule.
Outcomes	Pain scores at rest and movement-evoked; patients were also assessed for the incidence and severity of sedation, nausea, vomiting and pruritus. Patients were administered 3 questionnaires: a follow-up Hip Arthroplasty Pain questionnaire, The Neuropathic Pain Scale and The Hospital Anxiety and Depression Scale. Pain intensity was measured using a 0-10 numeric rating scale (NRS).
Notes	Preop: acetaminophen, celecoxib and dexamethasone; POP: acetaminophen, celecoxib and morphine PCA

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer-generated randomization schedule was used to assign patients at random in blocks of 6 to one of the 3 treatment groups".
Allocation concealment (selection bias)	Low risk	"The schedule was created by the hospital investigational pharmacy, which was otherwise not involved in the clinical care of the patients or in the conduct of the trial. The randomization schedule was kept in the pharmacy and none of the investigators had access to it".

Clarke 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Gabapentin and placebo medications were encapsulated in identically colored gelatin capsules and packaged in identical individual blister packs by the Sunnybrook Health Sciences Centre Investigational Pharmacy in order to maintain double-blind conditions".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Incomplete information
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data balanced across groups, but > 20%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Crousier 2008

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with long-term follow-up for 3 months
Participants	36 patients, no limit of age, requiring radical mastectomy with axillary dissection
Interventions	Ketamine 0.5 mg/kg previous to surgical incision + infusion during surgery at 0.25/mg/kg/h versus saline bolus + infusion
Outcomes	Pain scores, side effects profile
Notes	Co-analgesia: Morphine, acetaminophen/codeine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of the sequence generation is not reported
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment is not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The method to keep blinded the intervention is not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of the outcomes assessors at 3 months follow-up is unclear
Incomplete outcome data (attrition bias)	High risk	The proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate

Crousier 2008 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The trial was registered and non significant differences with the protocol were noticed
Other bias	High risk	25% (n:3/12) in the ketamine group versus 50% (9/18) in the placebo group, reported presurgical neuropathic pain

De Kock 2001

Study characteristics		
Methods	Single center, randomized, double-blind, 5 arms, placebo-controlled trial with long-term follow-up for 3 months	
Participants	100 Patients aged 55-75 undergoing curative surgical resection of rectal carcinoma	
Interventions	Control: saline infusion, Low IV dose: i.v. ketamine at the bolus dose of 0.25 mg/kg followed by an infusion of 0.125 mg/kg per h, High IV dose: 0.5 mg/kg and 0.25 mg/kg per h; Low epi dose: epidural ketamine 0.25 mg/kg and 0.125 mg/kg per h; high Epi dose: 0.5 mg/kg and 0.25 mg/kg per h.	
Outcomes	Cumulative morphine request up to 48 h after surgery; pain scores at rest and movement-evoked; area of hyperalgesia; global quality of analgesia management; Long term: any pain in the scar area and any unpleasant experience since the operation	
Notes	Co-analgesia: epidural bupivacaine, sufentanil, clonidine	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"According to a computer-generated table of random number assignments"...
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All studied solutions were prepared by an anesthesiologist who was not involved in the patient's care. The patient and the anesthesiologist who delivered anesthesia and evaluated analgesia also were blinded to the study solutions".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The incidence and importance of postoperative residual pain was evaluated at 2 weeks, 1 month, 6 months and 1 year after surgery. Patients were asked to answer the following questions…..This inquiry was performed by phone and confirmed by mail.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups and < 20%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Duale 2009

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with long-term follow-up for 6 weeks and 4 months
Participants	86 patients between 20 and 75 years of age scheduled for elective partial pneumonectomy under thoracotomy were considered for inclusion
Interventions	Racemic ketamine was diluted to 500 mg in 500 mL of isotonic saline.1 mL per kg of the solution was given 5 min before surgical incision, and 1 mL per kg/h until skin closure. For the postoperative period, 1 mg per kg of ketamine was diluted in isotonic saline in a 48 mL-syringe, then infused at the rate of 2 mL per h (i.e. 1 mg per kg for 24 h), then discontinued. In the placebo group, isotonic saline was given alone following the same protocol.
Outcomes	The primary endpoint was to assess whether ketamine was able to reduce the pain score at the 6th week after surgery, compared to placebo. The secondary endpoints were to compare the early postoperative pain parameters, the rate of side effects, the late parameters of pain and the quality of life between the 2 groups.Morphine consumption (in mg), pain at rest (VAS from 0 to 10), sedation (scale from 0 to 3), nausea, vomiting, dizziness, pruritus, sensation of dry mouth, and current vital parameters.Area of sensory abnormalities (hypoesthesia, allodynia, hyperalgesia. The neuropathic pain symptom inventory and the SF-36 were also filled out.
Notes	Co-analgesia: Before skin closure, the edges of the thoracotomy as well as the chest drainage orifices were infiltrated with 0.1% ropivacaine. In addition to the intraoperative ropivacaine infiltration, postoperative analgesia was ensured with interpleural 0.2% ropivacaine (40 mL into the chest tube clamped for 20 min), intravenous paracetamol (1 g every 6 h), nefopam (80 mg per 24 h in continuous infusion) and morphine. Ambulatory treatment of pain with acetaminophen/codeine.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation is not stated
Allocation concealment (selection bias)	Low risk	"Randomisation was undertaken by a research assistant who was not involved in the observations. An inclusion number was allocated randomly and kept in a sealed envelope".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"When the patient arrived at the operating theatre, the anaesthetist checked the randomisation, which was kept secret to the patient throughout the study".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All the observers of the study (i.e. nurses in recovery room and surgical ward, investigators and research assistants) were unaware of the treatment given, throughout the study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups
Selective reporting (reporting bias)	Low risk	Protocol was registered and no differences were noticed compared with publication
Other bias	High risk	Fewer than 50 patients per arm

Dullenkopf 2009

Study characteristics	
Methods	Single center, randomized, double-blind, 3 arms, placebo-controlled trial with long-term follow-up for 3 months
Participants	120 adult patients undergoing general or orthopedic operations anticipated to last 30 to 120 minutes
Interventions	The study medication for all 3 groups was prepared and blinded by the hospital pharmacist. A syringe containing 12 ml was provided for every patient. One ml of the study solution contained 1.5 mg, 5 mg or 0 mg of ketamine in groups Kl, Km and P, respectively. In all patients, 1 ml of the study solution was administered for every 10 kg of body weight, resulting in 0.15 mg/kg ketamine IV, 0.5 mg/kg ketamine IV or normal saline in groups Kl, Km and P, respectively.
Outcomes	Anesthetic consumption, time from skin closure to emergency, sedation score, ketamine side effects profile, pain management categorical score. At 3 months: pain scores at rest and movement evoked, pain management score from excellent to poor
Notes	Co-analgesia: novaminsulfone 1 gram + IV morphine and paracetamol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"On the basis of a computer-generated block randomisation"
Allocation concealment (selection bias)	Low risk	"The study medication for all 3 groups was prepared and blinded by the hospital pharmacist".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Solutions were prepared in a blinded fashion by the pharmacist
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients replied by mail 3 months later. Unclear if they were still blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	The proportion of missing outcomes (27.3%) compared with observed event risk enough to induce clinically relevant bias
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Eisenberg 2007

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with long-term follow-up for 1 and 6 months

Eisenberg 2007 *(Continued)*

Participants	22 Patients aged 18 to 75 years with breast cancer requiring mastectomy and axillary lymph node dissection. Subjects with any kind of chronic pain were excluded
Interventions	Treatment was initiated on the day before surgery and continued daily for 14 consecutive days. The dosing schedule was 100 mg of amantadine sulfate tablets twice daily. Patients in the placebo group received equal numbers of identical-looking placebo tablets according to the same schedule.
Outcomes	0-10 pain scores, rescue medications, multidimensional pain evaluation. 3 months evaluation: 0-10 pain intensity across 5 different anatomical areas, coanalgesia and non pharma treatments, chemotherapy, hormone or Rxtherapy, Short Form-McGill Pain Questionnaire, sensory examination at medical visit (1 month and 6 months)
Notes	Patients were allowed to use rescue medications, including opioids, simple analgesics (paracetamol or dipyrone), and non-steroidal anti-inflammatory drugs (NSAIDs)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was done in blocks of 4 according to a pre-prepared random code"...unclear how the sequence generation was created.
Allocation concealment (selection bias)	Unclear risk	Not stated in the publication
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Both the amantadine and the placebo tablets were supplied by Merz Co, Frankfurt, Germany"…unclear if the placebos matched the active drug.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. However the proportion of missing data was > 20%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Unclear risk	Fewer than 50 patients per arm

Fassoulaki 2001

Study characteristics

Methods	Single center, randomized, double-blind, placebo-controlled, 4 arms trial for 3 months
Participants	100 adult female patients, ASA I or II, scheduled for cancer breast surgery
Interventions	4 arms combining ropivacaine (brachial plexus + Intercostal infiltration); mexiletine 200 mg BID for 6 days starting the night before surgery, and placebos
Outcomes	Pain scores at rest and movement-evoked in the acute setting; Three months after surgery, all patients responded to a structured phone interview to determine if they had: radiotherapy and/or chemother-

Fassoulaki 2001 *(Continued)*

	apy; pain in the chest, axilla, arm of the operated side; reduced or absent sensation in the same areas; the average pain score (from 0 to 10) during the 3 months, if present; and the need for analgesics since they were discharged from the hospital.
Notes	Co-analgesia: propoxyfene and paracetamol; 24 hours after surgery: codeine + paracetamol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Three months after surgery, all patients responded to a structured phone interview to determine if they had…unclear if the interviewer was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups and < 20%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Fassoulaki 2002

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 3 months
Participants	75 ASA I or II female patients scheduled for breast surgery for cancer were recruited
Interventions	Patients were blindly randomized to one of 3 groups. In the mexiletine group, patients received 200 mg of mexiletine along with placebo capsules (identical in appearance to the gabapentin capsules) 3 times per day. Patients in the gabapentin group received 400 mg of gabapentin and placebo capsules (identical in appearance to the mexiletine capsules) 3 times per day. Patients in the placebo group received both placebo capsules 3 times per day. Administration of the active and/or placebo drugs started the evening before surgery and continued 3 times a day for the first 10 postoperative days, including the day of surgery.
Outcomes	The visual analog scale score assessed pain at rest and after movement. 3 months later, all patients were interviewed to identify intensity of chronic pain and analgesic requirements
Notes	Co-analgesia: propoxyfene and paracetamol
Risk of bias	

Fassoulaki 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Each patient was randomly assigned to a treatment group, and the first dose was given the evening before surgery"
Allocation concealment (selection bias)	Low risk	"Seventy-five envelopes were prepared, coded as Group 1, Group 2, and Group 3, sealed, and opened for each patient to indicate the group of assignment".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Envelopes, bottles with capsules, and coding were prepared by an anesthesiologist in cooperation with the hospital's pharmacy. This anesthesiologist did not participate in the study, evaluation of the patients or data, or in report of the findings."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Three months after surgery, patients were interviewed by phone to identify whether they received postoperative chemotherapy, radiotherapy, or both and if they experienced pain or abnormal sensations in the chest, axilla, or the arm of the operated side"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups and < 20%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Fransen 2006

Study characteristics	
Methods	Multicenter, randomized, double-blind, placebo-controlled trial for a variable follow up time (6-14 months)
Participants	902 Patients identified within 24 hours of completed THR (primary or revision), irrespective of age, reason for surgery, or procedure performed
Interventions	Ibuprofen 1200 mg Daily (TID) for 14 days
Outcomes	Primary outcomes: changes from baseline to follow-up in WOMAC. We standardised scores to a range of 0-10, with 0 indicating no hip pain or no difficulty with daily activities and 10 indicating severe hip pain or severe difficulty with daily activities. Secondary outcomes: Short form 36, compared with before surgery; hip status today with 5 response levels; frequency of use of analgesia for hip pain during the past week; ability to get "about the house" and ability to get "out of the house" with 5 response levels ranging from "not at all" to "no difficulty"; time spent participating in physical activity during the past week; objective measures of physical performance (hip flexion, time to walk 50 feet (about 15 metres), and timed "up and go"; radiographic evidence of ectopic bone formation according to the Brooker classification and major bleeding complications during hospital admission.
Notes	Co-analgesia was up to treatment group. No changes in the NSAIDs were allowed
Risk of bias	

Bias	Authors' judgement	Support for judgement

Fransen 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Randomisation was performed centrally by using a computer based system"
Allocation concealment (selection bias)	Low risk	"We used a minimisation program to stratify treatment by study centre and type of surgery performed (primary or revision). Treatment allocation was blinded and concealed from patients and study staff until the database was locked".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All study tablets were packaged in identical blister packs".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All assessments were standardised and performed blind to randomised treatment allocation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No statistical significant difference in the rate of dropouts. (P=0.06). The proportion of missing outcome data < 20%
Selective reporting (reporting bias)	Low risk	Protocol was registered and no differences were noticed compared with the publication
Other bias	Low risk	No other potential sources of bias were detected

Gianesello 2012

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for 2 days, 3 months and 1 year after surgery
Participants	60 adult patients of either sex, having American Society of Anesthesiologists physical status I-II, scheduled for elective decompressive lumbar laminectomy with spinal fusion for degenerative spinal stenosis.
Interventions	Patients were randomly assigned to 2 equal groups of 30 each using a computer-generated table of random numbers to receive either a matching PL or PG 300 mg (Lyrica; Pfizer) and PL or PG 150 mg, twice a day for 48 hours postoperatively.
Outcomes	Pain scores at rest and movement-evoked, Ramsay sedation scale, incidence of respiratory depression, hypotension and other side effects. Patients were called at 3 months to evaluate EuroQoL and perceived general health status.
Notes	Co-analgesia: intraoperative dexamethasone + POP morphine infusion and ketorolac

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to 2 equal groups of 30 each using a computer-generated table of random numbers".

Gianesello 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	"All of the medications were identical, were provided by the hospital pharmacy".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All of the medications were identical"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients were questioned during the first 1 hour in the postanesthesia care unit and were later evaluated in the ward at 4, 8, 12, 24, and 48 hours by an independent observer blinded to group allocation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Grigoras 2012

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with a daily follow-up for 7 days, and sensory examination 3 months after surgery
Participants	36 American Society of Anesthesiology physical status I or II patients undergoing breast surgery (mastectomy or wide local excision+axillary node dissection, including sentinel node mapping or clearance) were undertaken
Interventions	Immediately after orotracheal intubation, patients of the lidocaine group (L) received an IV bolus of lidocaine (1.5 mg/kg in 10 min) followed by a continuous IV infusion at 1.5 mg/kgh. The infusion was stopped 60 minutes after skin closure. Patients in the control group (C) received an equivalent saline regimen.
Outcomes	Visual analog scale (VAS) pain scores at rest and on arm movement was recorded at 2, 4, 24, 48, and 72 hours postoperatively, or at these time points until discharge from hospital; analgesic use was recorded for each group; A questionnaire was also used to assess the presence or absence of persistent pain, the time of onset, location and character of the pain, medications used for pain relief and impact on the patients' daily life, a history of chemotherapy or radiotherapy, and further surgery. PPSP was considered to be present if the answer to "Have you had pain in the last week which you attribute to your breast surgery?" was "Yes."; Three months postoperatively, patients had the area of peri-incisional hyperalgesia measured by the same blinded investigator and completed the short-form McGill Pain Questionnaire, the Pain Catastrophizing Scale, and the Hospital Anxiety and Depression Scale.
Notes	Intraoperative analgesia in both groups consisted of paracetamol IV 1 g, diclofenac IV 75 mg, and morphine sulphate PRN IV. Morphine was administered after induction of general anesthesia and titrated according to patient response to surgical stimuli.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Grigoras 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Patients were randomly allocated to 1 of 2 groups based on computer generated codes that were maintained in sequentially numbered opaque envelopes".
Allocation concealment (selection bias)	Low risk	"None of the investigators involved in patient management or data collection were aware of the group assignment".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"On the morning of surgery an anesthetist who was not involved in the patient's evaluation opened the envelope and prepared either 1% lidocaine or normal saline in coded 50mL syringes".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Three months postoperatively, patients had the area of peri-incisional hyperalgesia measured by the same blinded investigator"....
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study reported no missing outcome data at 3 months
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per group

Hayes 2004

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 3, 6 + 6 months after surgery
Participants	45 Patients presenting for above- or below-knee amputation because of peripheral vascular disease, cancer or chronic infection
Interventions	The Ketamine patients received a pre-induction intravenous (IV) bolus of ketamine 0.5 mg.kg–1, + IV infusion at 0.15 mg.kg/h. Control patients received a pre-induction IV bolus of normal saline, followed by IV infusion. Trial solutions were continued for 3 days postoperatively. If side-effects considered attributable to ketamine occurred (vivid dreams, hallucinations or confusion), the infusion rate was halved. If side-effects then continued or were severe, the infusion was ceased.
Outcomes	Opioid consumption at 24 and 72 hours, complications, patient satisfaction, phantom or stump pain incidence. 0-10 Pain scores (highest, lowest, usual and current level). Sensory examination with von Frey filaments including measurement of the area of sensitization.
Notes	Co-analgesia: morphine PCA. Amitriptyline and sodium valproate were used to treat phantom limb pain

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomized (via a random number generator) to receive"...

Hayes 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patient, anaesthetist, Acute Pain Service (APS) personnel, ward staff and investigators were blinded to the contents of the trial solution".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The patient, anaesthetist, Acute Pain Service (APS) personnel, ward staff and investigators were blinded to the contents of the trial solution".
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant proportion of missing outcome data (>20%)
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per group

Ilkjaer 2000

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 3 months after surgery
Participants	50 patients scheduled for non-malignant elective abdominal hysterectomy with a supravaginal, horizontal approach
Interventions	One hour before surgery, patients received dextromethorphan 150 mg or placebo (5 tablets) orally as premedication
Outcomes	Pressure pain detection threshold, von Frey pain detection threshold and hyperalgesia to von Frey hair stimulation proximal to the surgical wound, were assessed 3 months after the operation, during a control visit at the hospital.
Notes	Co-analgesia: intraoperative fentanyl. Postoperative: PCA morphine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study drugs (identical tablets of dextromethorphan 30 mg, or vehicle without dextromethorphan)".

Ilkjaer 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Excluded patients were replaced until 50 data sets were available for analysis
Selective reporting (reporting bias)	High risk	the authors reported sensory examination, however, it would be more clinical meaningful the report of pain scores or at least the rate of residual pain
Other bias	High risk	Fewer than 50 patients per group

Karanikolas 2011

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 6 months after surgery
Participants	65 patients > 18 yr with severe pain (VAS > 60 /100) one week before scheduled lower-limb amputation
Interventions	The study had five groups that received intravenous PCA Fentanil or Epidural fentanyl, which was started 2 days before surgery until the second postoperative day. One of the groups represented the "conventional analgesia" that included IM Meperidine and codeina/acetaminophen.
Outcomes	The results of the visual analog scale and the McGill Pain Questionnaire were recorded perioperatively and at 1 and 6 months
Notes	Patients received IV intraoperative remifentanil, too

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed using computer-generated blocks".
Allocation concealment (selection bias)	Low risk	"Each patient assigned to participate in the study had a sequentially numbered sealed envelope containing a randomization code. The envelopes were concealed until after consent was obtained".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"….control group patients had an epidural catheter placed subcutaneously at the L4 interspace in the lumbar area and received N/S at 2 ml/h. In addition, they had a second infusion pump that administered patient-controlled intravenous N/S".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...A second blinded investigator (G.M.) interviewed all patients before the beginning and after the end of the analgesic protocol (at 4- and 10-day and at 1- and 6-month follow-up), whereas a third blinded investigator (M.K.) conducted all interviews during the analgesic protocol (at least at 8-h intervals)".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were minimum and balanced across groups

Karanikolas 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol was registered and no significant differences were noticed compared with publication…except for the pain intensity inclusion criteria (> 70/100 in the protocol)
Other bias	High risk	Fewer than 50 patients per arm

Katz 2004a

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 3, 14 and 6 months after surgery
Participants	141 patients scheduled for radical prostatectomy for prostate cancer. Inclusion criteria were ASA I-II, age between 19 and 75 years
Interventions	Two 60 ml coded syringes were used labelled as pre-incision and post-incision. Every syringe had ketamine (1mg/ml) or saline. Group 1: PRE Ketamine POST: Saline; Group 2: PRE Saline POST Ketamine; Group 3: Both had saline. 10 minutes before incision. All patients received i.v. fentanyl (1 mcg/kg) every 80 min starting approximately 5 min before induction of general anesthesia. Approximately 10 min before skin incision, and after induction of general anesthesia, all patients received a bolus dose of i.v. fentanyl (0.5 mcg/kg). This was followed immediately by an i.v. bolus dose (0.2 ml/kg) and an i.v. infusion (0.0025 ml/kg/min) from the first syringe labelled 'pre-incision'. Seventy minutes after incision, the first infusion was stopped and all patients received a bolus dose of i.v. fentanyl (0.5 mcg/kg). This was followed immediately by an i.v. bolus dose (0.2 ml/kg) and an i.v. infusion (0.0025 ml/kg//min) from the second syringe labelled 'post-incision'. The second infusion was stopped after 80 min, approximately 150 min after incision.
Outcomes	Visual analogue pain scores at rest and movement (first 3 days); pain rating index, and present pain intensity. Touch and Pain Threshold using the von Frey filament (at 2 weeks follow up), Mental Health Inventory, Spielberg state-Trait Anxiety Inventory, At 6 months, patients were followed with the Follow-Up Questionnaire (FUPQ).
Notes	Co-analgesia: intraoperative IV fentanyl; PCA morphine after surgery

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A randomization schedule was computer-generated"…
Allocation concealment (selection bias)	Low risk	"An opaque envelope containing the patient number and group assignment was prepared, sealed and numbered for each patient by the hospital pharmacist".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. The anesthesiologist in charge of the case was also unaware of group allocation".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. The anesthesiologist in charge of the case was also unaware of group allocation".

Katz 2004a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	A proper method for incomplete outcome data was performed for analysis
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Low risk	No other potential sources of bias were detected

Kim 2010

Study characteristics		
Methods	Single center, randomized, double-blind, placebo-controlled trial for 3 months	
Participants	99 ASA class I–II patients, aged 20–65 years, with thyroid cancer were scheduled for elective robot-assisted endoscopic thyroidectomies and included in this study.	
Interventions	According to their assigned study group, patients received pregabalin 150 mg or placebo twice—1 h before surgery and 12 h after the initial dose. All pills were administered by a nurse who was not involved in the study.	
Outcomes	Pain scores, side effects profile, and incidence of anterior chest hypoesthesia	
Notes	Co-analgesia: intraoperative ketorolac and POP ibuprofen	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to one of 2 groups to receive….
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The drugs were provided by the hospital pharmacy as identical capsules to ensure blinding."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients, the surgeon, and the anesthesiologist responsible for follow-up during the postoperative period were blinded to group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups and < 20%
Selective reporting (reporting bias)	Low risk	Protocol was registered and no significant differences were noticed compared with publication
Other bias	Low risk	No other potential sources of bias were detected

Kinney 2011

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 3 months
Participants	120 patients aged 45 - 75 years undergoing elective thoracotomy
Interventions	Patients were allocated to receive either 600 mg of gabapentin or active placebo (diphenhydramine 12.5 mg) orally within 2 hours preoperatively
Outcomes	Pain scores in the acute setting + side effects of the medications. Telephone call: surgical site pain
Notes	Co-analgesia: thoracic epidural analgesia, POP fentanyl, ketorolac and acetaminophen

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Using a block randomization schedule stratified by surgeon…
Allocation concealment (selection bias)	Low risk	"All members of the surgical, nursing, and acute pain service teams were blinded to group assignment".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo capsules of identical shape and size to commercially available gabapentin were manufactured by the hospital pharmacy"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All outcome assessors were blinded to group allocation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups and < 20%
Selective reporting (reporting bias)	Low risk	Protocol was registered and no significant differences were noticed compared with publication
Other bias	Low risk	No other potential sources of bias were detected

Lakdja 1997

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 6 months
Participants	30 patients with adenocarcima requiring total or partial mastectomy with axillary dissection
Interventions	Ibuprofen: 400 mg 90 minutes before surgery, 2 h after and then q8h up to 32 hours after surgery
Outcomes	Pain Scores: VAS in the first 42 hours after surgery. At 6 months, consultation. They evaluated the need of adjuvant radiotherapy, the presence of dysesthesia, allodynia, paresthesia or hyperthesia that lasted more than 3 months and was present during the exam: SDPM: postmastectomy pain syndrome.

Lakdja 1997 *(Continued)*

Notes	Co-analgesia: 300 mcg of intraoperative fentanyl, POP analgesia: PCA morphine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups and < 20%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per group

Malek 2006

Study characteristics

Methods	Single center, randomized, double-blind (patients and outcomes assessor nurse), placebo-controlled trial for 6 months
Participants	100 women scheduled for breast cancer surgery
Interventions	Ketamine 1 mg/k/day in IV infusion for 2 days
Outcomes	After 6 months of surgery patients received a questionnaire concerning the presence of chronic pain, its intensity (1 - mild, 2-medium, 3 - strong, 4 - Unbearable), quality (constant vs intermittent), location (in scars, in the whole breast or chest wall, armpit, elsewhere) and nature (using the modified McGill Pain Questionnaire).
Notes	Co-analgesics: preoperative and postoperative meperidine + intraoperative sufentanil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drawing lots

Malek 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients were blinded. However, the person that prepared the solutions is unclear if he/she was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Patient filled out a questionnaire at 6 months. However is unclear if already knew what received during surgery
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Low risk	No other potential sources of bias were detected

Moore 2011

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 3 months
Participants	46 pregnant women 18 years or older, undergoing scheduled cesarean delivery
Interventions	600 mg of oral gabapentin 1 hour before the surgery
Outcomes	Pain scores, satisfaction with pain management, sedation, supplemental analgesia. At 3 months: sensory abnormalities and pain scores
Notes	Co-analgesia: IT morphine, intraoperative fentanyl, POP IV morphine, oral diclofenac, oral acetaminophen

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"According to a computer-generated randomization…
Allocation concealment (selection bias)	Low risk	"According to a computer-generated randomization table known only to the pharmacy department, the gabapentin or placebo capsules were then placed in sequentially numbered envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...identical blue capsule covers".
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported

Moore 2011 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data balanced across groups; however, the missing outcome data is > 20%
Selective reporting (reporting bias)	Low risk	Protocol was registered and no significant differences were noticed compared with publication
Other bias	High risk	"The study was terminated after 46 patients because a very low recruitment rate led to prolongation of the study".

Nikolajsen 2006

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 3 and 6 months
Participants	46 adults undergoing lower limb amputation because of peripheral vascular disease
Interventions	Patients received one capsule (300 mg gabapentin or placebo) on the first postoperative day, 3 capsules (900 mg) on days 2–4, 4 capsules (1,200 mg) on days 5 and 6, 5 capsules (1,500 mg) on days 7 and 8, 6 capsules (1,800 mg) on days 9 and 10, seven (2,100 mg) capsules on days 11 and 12, and eight capsules (2,400 mg) on days 13–30. Patients with a creatinine clearance 30 ml/min but 60 ml/min received a maximum dose of 1,200 mg. If patients experienced intolerable side effects before the maximum dose of 1,200/2,400 mg was reached, they were allowed to stay on a lower dose for the rest of the study period. Patients who did not tolerate a minimum dose of 900 mg were withdrawn from the study.
Outcomes	Phantom limb and stump pain scores, McGill pain questionnaire, guessing about treatment
Notes	Epidural Infusion of bupivacaine and opioid + paracetamol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"….using a computer-generated randomization list in block sizes of 8 and 10".
Allocation concealment (selection bias)	Low risk	"During the study, the randomization list was held securely at the hospital pharmacy and released only after study completion".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"After 30 days of treatment, 10/39 patients correctly identified the treatment given".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In 5 cases, the investigator correctly identified the treatment given: gabapentin: side effects (n = 3); placebo: lack of effect (n = 2). In 8 cases, the answers were incorrect, and in 26 cases the treatment could not be identified
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant number of drop outs (26.1%) and incomplete treatments

Nikolajsen 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Small sample size, pain intensity was low in both treatment groups; fewer than 50 pts per arm

Perrin 2009

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 1, 2; long term FU: 6 months after surgery
Participants	12 patients booked for elective unilateral total knee arthroplasty with an ASA I to III
Interventions	A programmed syringe delivered ketamine 0.5 mg/kg bolus followed by 4 µg/kg/min infusion, or equivalent volumes of the saline solution. The infusion commenced before surgical incision and continued until the surgical wound was bandaged or the syringe was empty.
Outcomes	Numerical rating scale pain scores at rest and movement (pressure care turning) were collected at 4, eight, 12, 16 and 20 hours post intrathecal injection and averaged to give a first 24-hour pain 'score' with a denominator of 10. The next 5 pain enquiries from 24 to 40 hours were poorly recorded and are not presented. 48 h morphine request; Primary outcome measures 1. Incidence of pain at 6 months equal to or worse than that preoperatively using WPS; 2. Incidence of zero pain in operated knee at 6 months using WPS; 3. Presence of pain not meeting the above criteria, arbitrarily labelled mild/moderate.
Notes	Paracetamol 750 mg 24h, PCA morphine, ibuprofen 800 mg PRN

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	The sealed syringe code was stored in our pharmacy department
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The publication states that the study is triple blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant number of drop outs (25%) and incomplete treatments
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated

Perrin 2009 *(Continued)*

Other bias	High risk	Fewer than 50 patients per arm

Pesonen 2011

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for one and 3 months
Participants	Seventy patients, aged 75 yr or older and undergoing primary elective coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) or single valve repair or replacement with CPB, were initially included in the study.
Interventions	Beginning on the first postoperative morning, patients received 75 mg pregabalin or placebo twice daily until the fifth postoperative day.
Outcomes	Pain scores, Richmond Agitation, Sedation Score, oxycodone consumption, ICU stay, paracetamol requirement
Notes	Co-analgesia: paracetamol, oxycodone

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"pharmacy performed the randomization using a computer generated randomization schedule"
Allocation concealment (selection bias)	Low risk	"Each consenting patient received the study drug according to a consecutive randomization number, which was labelled to opaque plastic containers containing the study drugs".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The pharmacy also prepared the study medication by packing pregabalin or placebo into identical capsules for blinding".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The Verbal Rating pain score at rest and during movement and the analgesics consumed were recorded in a telephone interview by a blinded interviewer 1 and 3 months after the surgery".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups and < 20%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Remerand 2009

Study characteristics

Remerand 2009 *(Continued)*

Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 1, 14, 30, 90 and 6 months after surgery
Participants	154 adult patients scheduled for a total hip arthroplasty
Interventions	Patients received an IV bolus of 0.5 mg/kg ketamine (maximum 50 mg) from the first blinded 5-mL syringe, followed by a 24-h infusion using the second study syringe at 2 mL/h (equivalent to 2 mcg/Kg/min).
Outcomes	"Morphine consumption during the first 24 postoperative hours was our primary outcome".
Notes	Co-analgesia: intraoperative sufentanil, POP paracetamol, ketoprofen, PCA morphine (day 1), oral morphine (day 2-4)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	" as part of a computer generated randomization process"....
Allocation concealment (selection bias)	Low risk	"160 identical white envelopes were prepared, numbered, and sealed by a person external to our clinical unit. Each envelope contained detailed instructions of the preparation of 2 syringes (ketamine or saline). On the morning of the THA, a nurse prepared 2 syringes as described in the instructions, left them in a sterile box, and had no further clinical or research involvement".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Nurses, anesthesiologists, and surgeons were unaware of the group assignment until the end of the study".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Patients were interviewed by phone on Days 30, 90, and 180 for pain location and intensity (at rest and while walking), need for help when walking, and analgesic consumption, by 1 of the 2 first authors". Insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The study size was then set at 80 patients per group, to compensate for possible dropout patients and the fact that randomization was not created in blocks. In case of incomplete follow-up, missing data were excluded from analysis, but the remaining data (before any missing phone interview) were analyzed".
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Low risk	No other potential sources of bias were detected

Romundstad 2006

Study characteristics

Methods	Single center, randomized, double-blind, 3 arms, placebo-controlled trial with follow-up for days 6 weeks and 1 year after surgery

Romundstad 2006 *(Continued)*

Participants	219 patients (20-45 yo) underwent breast augmentation surgery
Interventions	Single i.v. preoperative dose of methylprednisolone 125 mg, parecoxib 40 mg or saline
Outcomes	The primary outcome variable was prevalence of pain at rest. Secondary outcome variables were prevalence of evoked pain, and sensory changes.
Notes	Intraoperative: fentanyl + infiltrative (intercostal) Lidocaine+adrenaline. POP: acetaminophen 500 mg/ codeine 30 mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A person not involved in the treatment and follow-up of patients randomized the patients in blocks of nine to 1 of 3 groups of equal size using a list of random numbers, according to the Moses-Oakford algorithm".
Allocation concealment (selection bias)	Low risk	"Block size and randomization code were not revealed to the investigators until all measurements and calculations had been entered into the database".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Methylprednisolone (Solu-Medrol) 125 mg, parecoxib 40 mg, and placebo (NaCl) were prepared at Rikshospitalet University Hospital by a doctor not in contact with the observers or patients. Test drugs were diluted with saline to fill a 10-mL syringe, marked with patient number and the possible test drugs, and appeared identical for all persons involved in the trial".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the person conducting the interview nor the patients were aware of the group to which the patients were assigned".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Low risk	No other potential sources of bias were detected

Schley 2007

Study characteristics

Methods	Single center, randomized, double-blind, placebo-controlled trial with a long term FU up to 6 months
Participants	19 patients scheduled for amputation of at least one finger
Interventions	Memantine: First week: 10 mg/day; second week: 20 mg/day; Week 3 and 4th: 30 mg/day versus placebo matched pills
Outcomes	Primary outcome variable was intensity of Phantom Limb Pain (PLP). Secondary outcome parameters were prevalence PLP, intensity of stump pain, phantom sensation and stump sensation. Intensity of these sensations was recorded via visual analogue scale (VAS 1–100) upon (1) admission; (2) before pri-

Schley 2007 *(Continued)*

	mary block; (3) 30 min after primary block; (4) twice daily during hospitalization; (5) 4 weeks after end of memantine treatment; (6) 6 and 12 months after end of memantine treatment.
Notes	Co-analgesia: brachial plexus block for one week after the amputation. Intraoperative sufentanil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and treating physicians were blinded for the medication".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	…..Also data acquisition and processing were performed in a blinded fashion
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9/30 patients patients redraw their agreement briefly after beginning of the treatment. Reasons are not stated
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Unclear risk	Before the beginning of treatment (admission) 11 of 19 patients (58%) had developed PLP: 6 patients (60%) in memantine group and 6 patients in the control group.

Sen 2009

Study characteristics

Methods	Single center, randomized, double-blind, placebo-controlled trial for 3 and 6 months
Participants	Sixty male patients – aged 20–40 years, ASA I – who were scheduled for unilateral elective indirect inguinal herniorrhaphy under spinal anaesthesia
Interventions	In the gabapentin group, a single dose of 1.2 g oral gabapentin was given to patients 1 h before surgery; in the placebo group, a placebo capsule was given 1 h before surgery.
Outcomes	Pain scores, side effects, sedation, nausea, vomiting
Notes	Co-analgesia: tramadol in PCA for 24 h. Rescue analgesia with diclofenac

Risk of bias

Bias	Authors' judgement	Support for judgement

Sen 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	"randomly allocated into 2 groups (according to computer-generated randomization)".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All measurements were recorded by the same anaesthesiologist who was blinded to the study groups".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Assessment of postoperative pain at 1, 3 and 6 months was carried out – via telephone – with an 11-point numerical rating scale (NRS); 0 indicating 'no pain' and 10 indicating 'worst pain imaginable'".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimum missing outcome data
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Sen 2009a

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for 3 and 6 months
Participants	Sixty women scheduled for abdominal hysterectomy
Interventions	The patients were assigned to 1 of the 3 treatment groups. The control group received oral placebo capsules and bolus plus infusion of saline; the ketamine group received oral placebo capsules and, before incision, 0.3 mg/kg IV bolus and 0.05 mgkg1h1 infusion of ketamine until the end of surgery11; and the gabapentin group received oral gabapentin 1.2 g and bolus plus infusion of saline.The initial dose of the study medication was administered 1 h before surgery.
Outcomes	Pain scores, sedation scale, morphine requirement, recovery of bowel function, patient satisfaction
Notes	Co-analgesia: intraop morphine + morphine PCA + codeine acetaminophen

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The patients were randomly assigned to 1 of the 3 treatment groups using a computer-generated table".
Allocation concealment (selection bias)	Low risk	"All study drugs were prepared by the hospital pharmacy, and an appropriate code number was assigned to each patient".
Blinding of participants and personnel (performance bias)	Low risk	"The same label was used for all the infusions for blinding purposes".

Sen 2009a *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All measurements were recorded by a research assistant who was blinded to the study medication. Patients were also contacted by one of the investigators at 1, 3, and 6 mo after discharge to inquire as to when they were able to resume normal activities of daily living (i.e., return to work) and if they had any residual postoperative (incisional) pain".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Spreng 2010

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with scheduled follow ups at 7 and 90 days after surgery
Participants	77 patients > 18, ASA I-II scheduled for day-care elective hemorrhoidectomy
Interventions	Approximately 1 h before surgery all patients received oral paracetamol 1-2 grams. Total Intravenous Anesthesia (remifentanil +propofol) was the anesthesia technique. During operation all patients received intravenous 8mg dexametahasone and 30mg ketorolac. After surgery, the surgeon injected 10–20 ml bupivacaine 2.5mg/ml + epinephrine in the surgical field. After insertion of laryngeal mask, but before start of surgery, patients in the (S)-ketamine group received an intravenous bolus dose of 0.35mgkg (S)-ketamine (Pfizer, 2.5mgml−1) followed by continuous infusion of 5gkg−1 min−1 (S)-ketamine. Patients in the placebo group received an equivalent volume of isotonic saline (bolus and infusion). Rescue pain medication was fentanyl 0.05–0.1mg IV during 0–30 min after end of surgery and paracetamol + codeine (500mg+ 30mg) orally later on; and was given when VAS > 30, NRS > 3 or upon patient request.
Outcomes	VAS (0-100) pain scores and numerical rating scales (0-10). At 30 min after the end of surgery the patients completed the trail making test for evaluation of (S)-ketamine psychotomimetic side-effects: patient is asked to connect randomly distributed numbers (from 1 to 25) as fast as possible. At discharge from the PACU patients' grade of satisfaction was registered (satisfied–indifferent–not satisfied) and need of rescue analgesics in the PACU was documented. The patients were interviewed by phone on postoperative day 1, day 7 and 3 months after surgery; assessing pain intensity, need for analgesics, grade of satisfaction and side-effects (nausea, hallucinations, double and/or abnormal colour vision).
Notes	Dexamethasone was administered at analgesic range + local analgesia infiltration, which increases the external validity of the results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation is not stated

Spreng 2010 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Permuted block randomization, blinding and packing of the study medication were performed by the hospital pharmacy. The randomization codes were provided in sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients in the placebo group received an equivalent volume of isotonic saline (bolus and infusion)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	...."They were observed and evaluated by nursing staff which were blinded to the treatment. Pain intensity was assessed after 15, 30, 60 min and before discharge from PACU using visual analog scale (VAS, 0–100) and numeric rating scale (NRS, 0–10) for pain".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Compensating for missing data a total of 80 patients was planned for this study. However, It is unclear what proportion of patients was effectively contacted at the 3 months follow-up
Selective reporting (reporting bias)	Low risk	The protocol was registered and the primary outcome fits with the primary outcome of the publication
Other bias	High risk	Fewer than 50 patients per arm

Suzuki 2006

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 1, 2, 30, 90 and 180 days after surgery
Participants	50 patients who were scheduled to undergo open thoracotomy
Interventions	Before Anesthesia induction, an epidural inserted and confirmed with ropivacaine. After tracheal intubation, an intravenous infusion of 0.05 mg/kg/h ketamine or placebo at the same volume was started. The infusion rate of ketamine was determined by simulation in a target-controlled infusion program to maintain a blood concentration of 20 ng/ml. After surgery, all patients received a continuous epidural infusion of 0.05 mg/ml morphine and 0.15% ropivacaine at an initial rate of 3 ml/h or by an infusion pump. Epidural infusion was continued for 48 h. All patients continued to receive infusion of ketamine or placebo for 72 h after surgery. If the patient requested additional analgesia within 24 h of surgery, 50 mg intravenous flurbiprofen was administered.
Outcomes	The primary endpoint of the study was the number of patients who felt baseline pain at 3 months after thoracotomy. In a long term, the outcomes were the number of patients who felt usual pain at 1, 3, and 6 months after surgery; the number of patients who were taking pain medication 1, 3, and 6 months after surgery; the number of patients who felt an unpleasant sensation on the surgical wound; and the number of patients who felt inconvenienced by the wound.
Notes	Co-analgesia: epidural analgesia (ropivacaine + morphine for 48 hours)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were assigned to one of 2 groups using a computer-generated randomization schedule".

Suzuki 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study drug, ketamine or placebo, was prepared and placed in the infusion pump by an investigator who did not participate in the administration of anesthesia or the evaluation of postoperative pain.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At 1, 3, and 6 months after surgery, one of the investigators, who did not know the group assignment, called each patient's home and administered the same questionnaire that had been given on day 7.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimum missing outcome data (12% only)
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	Fewer than 50 patients per arm

Sveticic 2008

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 1, 2, 90 and 180 after surgery
Participants	352 patients undergoing major elective orthopedic surgery
Interventions	Morphine PCA + ketamine (1mg:1mg). Boluses of 1.5 mg of each drug, max. 6 per 4
Outcomes	Primary outcome: rate of unsatisfactory treatment; secondary outcomes: mean pain scores at rest and movement-evoked; analgesic consumption; side effects profile; and incidence of pain at 3 months and 6 months
Notes	Co-analgesia: intraoperative fentanyl; mepivacaine (50 ml) for nerve blockade or bupivacaine for spinal anesthesia; POP IV propacetamol + morphine PCA and ketorolac

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed by drawing lots immediately before administering the solution".
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly allocated to receive PCA consisting of either morphine 1.5 mg (Group M) or morphine with ketamine 1.5 mg of each"…..Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patients, nurses who cared for patients, anesthesiologists who performed the anesthesia were not aware of the PCA drug used".

Sveticic 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators who gathered the data were not aware of the PCA drug used".
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 25.9% and 10.2% of all patients returned our chronic pain questionnaire 3 and 6 mo after the surgery, respectively
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	Low risk	No other potential sources of bias were detected

Ucak 2011

Study characteristics	
Methods	Single center, randomized, double-blind, placebo-controlled trial for one, 3 and 6 months
Participants	40 patients (34 men and 6 women) who were less than 80 years of age and undergoing elective CABG surgery with cardiopulmonary bypass (CPB) were enrolled.
Interventions	The gabapentin group received orally 1.2 g/d 1 h before and 2 days after surgery, and the placebo group received a placebo capsule instead.
Outcomes	Pain scores, tramadol request, side effects, and pop morbidities
Notes	IV tramadol and acetaminophen

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The patients were assigned randomly into 2 groups (using a computer- generated table)".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A single nurse who was blinded to the study protocol prepared the placebo capsules and administered them to the patients. The doctors and nurses in the operating room, intensive care unit, and ward were blinded to the study protocol".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"All patients completed a 1- and 3-month follow-up. The assessment of postoperative pain at 1 month was performed at the outpatient visits, and at 3 months it was carried out via telephone with a 10 point numeric rating scale".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated

Ucak 2011 *(Continued)*

Other bias	High risk	Fewer than 50 patients per arm

Weis 2006

Study characteristics		
Methods	Single center, randomized, double-blind, placebo-controlled trial with follow-up to 6 months after surgery	
Participants	36 high-risk patients undergoing cardiac surgery	
Interventions	Hydrocortisone: loading dose (IV 100 mg) before induction, followed by a infusion of 10 mg/h for 24 hours, which was reduced to 5 mg/h POD 2 and then tapered to 3X20 mg IV on POD 3 and 3 X 10 mg IV on day 4	
Outcomes	Acute period: Inotropic agents use and acute phase reactants. At 6 months the patients were contacted by telephone and received a detailed re-explanation of the purpose of the study. The authors measured SF-36, traumatic memories and chronic stress symptoms.	
Notes	Co-analgesia is not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The patients were randomly assigned to one of 2 treatment groups with the use of a computer-generated randomization list
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	….received normal saline in identical vials in a double-blind fashion. The vials were prepared by a study nurse who was not involved in the care of patients participating in the trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients returned questionnaires to the authors….
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data > 20%
Selective reporting (reporting bias)	Low risk	Outcomes reported are clinically meaningful and validated
Other bias	High risk	The paper is unclear about the number of patients with any pain at 6 months. Fewer than 50 patients per arm

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arcioni 2007	The study evaluated regional/local techniques for analgesia
Bell 2001	The study evaluated regional/local techniques for analgesia
Biyik 2009	Open label study
Bone 2002	Not preventive study; pain is already established
Buvanendran 2003	Patients were followed for less than 3 months
Camilleri 2001	The study used a population out of the scope of the review (non surgical/late postsurgical setting)
Capdevila 1999	The study reported outcomes in the acute setting only
Chiu 2008	The study evaluated regional/local techniques for analgesia
Clarke 2010	The study is a secondary analysis of Clarke 2009
Cobellis 2004	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Cohen 2006	The study evaluated regional/local techniques for analgesia
Elkaradawy 2012	The study randomized a regional/local technique for analgesia. Gabapentin was administered for patients reporting moderate/severe pain
Essving 2009	The study evaluated regional/local techniques for analgesia
Essving 2010	The study evaluated regional/local techniques for analgesia
Fassoulaki 2000	The intervention consisted of a topical intervention that is out of the scope of the review
Fassoulaki 2005	This study combines a systemic analgesic (gabapentin) and topical analgesia. It is not possible to 'weight' the effectiveness of each intervention due to methodological issues
Fassoulaki 2006	Patients were followed for less than 3 months
Fassoulaki 2007	Patients were followed for less than 3 months
Fransen 2004	This is the publication of a protocol
Guan 2005	The study reported pain scores in the short term, only; for the long-term follow-up, the study reported range of motion
Gupta 2006	The study evaluated regional/local techniques for analgesia
Harding 1991	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Hartrick 2011	Patients were followed for less than 3 months
Honigmann 2007	The study evaluated regional/local techniques for analgesia
Huse 2001	Cross-over study that explored the impact of morphine sulfate in pain scores and sensory findings. Patients included were already amputated
Jaeger 1992	Cross-over study

Study	Reason for exclusion
Jirarattanaphochai 2007	The study evaluated regional/local techniques for analgesia
Kadic 2009	The study evaluated regional/local techniques for analgesia
Kamencic 2008	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Kampe 2003	The study evaluated regional/local techniques for analgesia
Katz 2004	The study evaluated regional/local techniques for analgesia
Kim 2011	Patients were followed for less than 3 months
Kollender 2008	The study reported outcomes in the acute setting only
Koninckx 2008	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Lambert 2001	The study evaluated regional/local techniques for analgesia
Lampl 2002	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Lavand'homme 2005	The study has no placebo group
Lynch 2003	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Maier 2003	Not preventive study; pain is already established
Martin 2008	The study evaluated regional/local techniques for analgesia
Morin 2005	The study evaluated regional/local techniques for analgesia
Nehler 2007	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Nesher 2008	The study reported outcomes in the acute setting only
Nesher 2009	The study reported outcomes in the acute setting only
Nikolajsen 1997	The study evaluated regional/local techniques for analgesia
Nikolajsen 2000	Not preventive study; pain is already established
Nissman 2008	Patients were followed up for less than 3 months
Obata 1999	The study evaluated regional/local techniques for analgesia
Parker 2006	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Perniola 2009	The study evaluated regional/local techniques for analgesia
Reuben 2004	Retracted publication
Reuben 2005	Retracted publication
Reuben 2006	Retracted publication
Reuben 2007	Retracted publication

Study	Reason for exclusion
Reuben 2008	Retracted publication
Rhodes 1988	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Ryu 2011	The study evaluated regional/local techniques for analgesia
Salengros 2010	The study is not placebo controlled
Sanders 2009	The study evaluated regional/local techniques for analgesia
Senturk 2002	The study evaluated regional/local techniques for analgesia
Sesti 2007	The study used a population out of the scope of the review (non-surgical/late postsurgical setting)
Singh 2007	The study evaluated regional/local techniques for analgesia
Solak 2007	Not preventive study; pain is already established
Tramer 1996	Patients were followed up for less than 3 months
Wai 2010	The study evaluated the local administration of morphine, this review is focused in the impact of systemic analgesia
Waikakul 1999	Open label trial
White 2007	Patients were followed up for less than 3 months
Wu 2008	Not preventive study; pain is already established

Characteristics of studies awaiting classification *[ordered by study ID]*

Bilgen 2012

Methods	Double blind, randomized trial
Participants	One hundred and forty term pregnant women undergoing elective Cesarean delivery
Interventions	Participants were randomized into four groups (N=35 each), placebo (0.9% normal saline), ketamine 0.25, 0.5, or 1 mg kg(-1) intravenously
Outcomes	Patients were evaluated for persistent postoperative pain at 2 weeks, 1 and 6 months, and 1 year.
Notes	

Cohen 2013

Methods	Multicenter, randomized, controlled trial
Participants	Seventy-seven patients undergoing inguinal hernia surgery
Interventions	Subcutaneous etanercept 50 mg administered 90 minutes before surgery vs. saline

Cohen 2013 *(Continued)*

Outcomes	The primary outcome measure was a 24-hour numerical rating scale pain score. Secondary outcome measures were postanesthesia care unit pain scores, 24-hour opioid requirements, time to first analgesic, and pain scores recorded at 1 month, 3 months, 6 months, and 12 months.
Notes	

Fassoulaki 2012

Methods	Randomised controlled trial.
Participants	Eighty patients scheduled for abdominal hysterectomy or myomectomy
Interventions	The pregabalin group received 150 mg of pregabalin 8-hourly, starting on the afternoon before surgery and continued until the fifth postoperative day. The control group was similarly treated, but received placebo capsules instead.
Outcomes	One and 3 months postoperatively patients were interviewed for the presence of pain and analgesic needs due to surgery.
Notes	

Martinez 2013

Methods	Randomized, double-blind, controlled study.
Participants	One hundred patients undergoing scheduled lumbar discectomy
Interventions	The minocycline group received 100mg minocycline orally, twice daily, beginning the evening before surgery and continuing for 8days.
Outcomes	The primary outcome was the change in lower limb pain intensity at rest between baseline and 3months. Secondary outcomes were pain intensity on movement, the incidence of persistent pain and chronic neuropathic pain, back pain intensity at rest and on movement, and changes in Neuropathic Pain Symptom Inventory, Brief Pain Inventory, and Roland-Morris scores at 3months.
Notes	

Mendola 2012

Methods	Randomized, double-blind study.
Participants	Sixty-six patients undergoing thoracotomy
Interventions	Thirty-three patients received an i.v. infusion of S(+)-ketamine (Group S(+)K) for 60 hours and 33 patients received i.v. placebo (Group PLAC)
Outcomes	Neuropathic Pain Symptom Inventory (NPSI) was evaluated at 1, 3 and 6 months.
Notes	

NCT00224588

Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients eligible for thoracotomy or pneumectomy
Interventions	Drug: Ketamine
Outcomes	Primary outcome measures: post thoracotomy pain at 2 months assessed using a french equivalent of the McGill Pain score and pain area measurements. Secondary outcome measures: Analogic pain scores at rest and after coughing
Notes	This study has been completed.

Short 2012

Methods	Randomized, double-blind, placebo-controlled dose-finding trial.
Participants	One hundred and thirty-two women undergoing elective cesarean delivery
Interventions	Participants were randomized into 3 groups to receive 300 or 600 mg oral gabapentin, or placebo, 1 hour before surgery.
Outcomes	The primary outcome was pain on movement at 24 hours. Secondary outcomes included satisfaction with analgesia, supplemental opioid consumption, lactation difficulties, neonatal outcomes, maternal sedation, and other adverse effects. Three months after delivery, patients were contacted for assessment of chronic pain.
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

NCT00129597

Study name	Effect of Ketalar to Prevent Postoperative Chronic Pain After Mastectomy
Methods	Randomized, double-blind, clinical trial
Participants	Adult Patients (18-80), ASA I-II Exclusion criteria: heart, hepatic or renal failure; allergy to study medications; psychiatric disease; chronic antalgic treatment
Interventions	Ketalar (further information is unclear)
Outcomes	Primary outcome measures: pain intensity 3 months after mastectomy Secondary outcome measures: impact on life quality; area of hyperalgesia
Starting date	December 2004
Contact information	Vincent, PIRIOU, MD

NCT00129597 *(Continued)*

Notes	The recruitment status of this study is unknown because the information has not been verified recently. Verified March 2007 by Hospices Civils de Lyon. Recruitment status was active, not recruiting

NCT00442546

Study name	Efficacy And Safety Of Pregabalin For Pain Following Total Knee Replacement
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: Adult patients (ASA I-III)with osteoarthritis (OA) undergoing elective primary TKA under regional anesthesia (neuroaxial with or without peripheral nerve block) Exclusion criteria: bilateral procedure or revision; subjects with chronic inflammatory conditions or any other chronic pain disorder
Interventions	Pregabalin 150 mg/day, 300 mg/day or placebo
Outcomes	Primary Outcome Measures: Subject Reported Worst 0-10 Pain Score in Daily Diaries Using the Worst Pain Item of the Modified Brief Pain Inventory - Short Form (m-BPI-sf) Long term Secondary Outcome Measures (at 3 & 6 months): Pain Interference Index Score as Measured by the m-BPI-sf; Pain Interference With Relations With People; Pain Interference With Enjoyment of Life; pain Interference With General Activity; pain Interference With Mood; Pain Interference With Walking Ability; pain Interference With Normal Work; Pain Interference With Sleep: number of Subjects With Persistent Pain Based on 11-Point Verbal Rating Scale (VRS); Neuropathic Pain Symptom Inventory (NPSI).
Starting date	May 2007
Contact information	Pfizer CT.gov Call Center
Notes	This study has been completed (First Received on March 1, 2007. Last Updated on February 15, 2011)

NCT00468845

Study name	Study Of The Efficacy And Safety Of Pregabalin Compared To Placebo For Treatment Of Post-Surgical Pain From Hysterectomy
Methods	Randomized, double-blind, clinical trial
Participants	Patients (ASA I-II)undergoing elective total abdominal hysterectomy using a transverse incision with or without bilateral salpingo-oophorectomy. The subject is expected to remain at the hospital (or intermediate care facility) for a minimum of 2 days following surgery; Exclusion Criteria: vaginal hysterectomy; use of nerve block, spinal anesthesia or epidural anesthesia for post-surgical pain control; Subjects who have been using any opioid medications 2 weeks or more continuously within 3 months prior to the screening visit; NSAIDs users.
Interventions	Pregabalin (Lyrica) 150 mg/day, 300 mg/day double-blind or matched placebos
Outcomes	Primary Outcome Measures: Worst Pain Using the Modified Brief Pain Inventory at day POP 2. Secondary Long-term Outcome Measures: Incidence of Chronic Post-operative Pain [Time Frame: 3

NCT00468845 *(Continued)*

	and 6 Months PS]Chronic post-operative pain as a result of abdominal hysterectomy as reported by participants on PS questionnaire of pain within last 24 hours in area affected by surgery.
Starting date	June 2007
Contact information	Pfizer
Notes	This study has been completed. First received on May 1, 2007. Last updated on June 7, 2011

NCT00551135

Study name	Surgical Pain After Inguinal Hernia Repair (SPAIHR)
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients undergoing primary open unilateral inguinal herniorrhaphy (hernia repair), using mesh Lichtenstein surgery procedure and under general anesthesia; patients must be able to use and tolerate non-steroidal anti-inflammatory drugs (such as naproxen), tramadol, oxycodone, and acetaminophen/paracetamol for pain control after surgery. Exclusion criteria: emergency surgery; use of nerve block or spinal/epidural/paravertebral anesthesia; subjects that are not allowed to receive the anesthesia agents indicated per protocol and general anesthesia.
Interventions	Pregabalin 25 mg BID, or 75 mg BID or 150 mg BID or placebo
Outcomes	Primary outcome measures: Modified Brief Pain Inventory-Short Form (mBPI-sf): Worst Pain 24 Hours Post Surgery. A self-administered 11-point Likert rating scale to rate pain in the past 24 hours. Secondary long-term outcome measures (3 & 6 months after surgery): Number of participants who reported surgery-related pain at assessment; Pain Severity Index Score and Pain Interference Index Score on the Modified Brief Pain Inventory-Short Form (mBPI-sf); Total Score and Subscale Scores Using the Neuropathic Pain Symptom Inventory (NPSI).
Starting date	January 2008
Contact information	Pfizer
Notes	This study has been completed. First Received on October 26, 2007. Last Updated on June 8, 2010

NCT00583869

Study name	Role of Pregabalin in Treatment of Post-Op Pain in Fracture Patients (LYRICA)
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients (19-70) with fractures requiring operative treatment during a single operative episode Exclusion criteria: history of opioid abuse/misuse; contraindications to pregabalin or narcotic analgesics; closed head injury; psychiatric illness requiring medical treatment; surgery for other injuries (splenectomy, etc); history of seizures requiring current anticonvulsant therapy.

NCT00583869 *(Continued)*

Interventions	Placebo group: Two hours before surgery, patients will receive 75mg of pregabalin. Patients will be placed on a patient-controlled anesthesia pump (PCA) for 24 hours. On post-operative day one, the patients will be switched to oral oxycodone as needed with supplementation with IV Demerol for breakthrough pain. In addition, patients will receive a placebo PO BID or pregabalin 75 mg or pregabalin 150 mg beginning on the day of surgery until discharge.Upon discharge, the patient will be given study medication (placebo PO BID or pregabalins). Rescue medications will be allowed during the study (including post-operative and outpatient periods). Outpatient rescue medications will consist of hydrocodone/APAP 7.5mg PO Q6H PRN.
Outcomes	Primary outcome measures: Amount of pain medication in morphine equivalent units used during the hospitalization Secondary outcome measures: pain scores at 3 months
Starting date	May 2007
Contact information	David A. Volgas, MD, Associate Professor of Surgery, The University of Alabama at Birmingham
Notes	This study is ongoing, but not recruiting participants. First received on December 21, 2007. Last updated on September 15, 2010

NCT00618423

Study name	The Effect of Perioperative Ketamine on Acute and Chronic Pain After Major Back Surgery (KetaDol)
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: Adults, ASA I-III, undergoing back surgery (laminectomy, lumbar arthrodesis (Posterior Lumbar Interbody Fusion - PLIF, Transforaminal Lumbar Interboby Fusion - TLIF, Postero-lateral Fusion, semi-rigid fixation. Exclusion Criteria: heart disease, glaucoma, allergy to study drugs, dementia, failed back surgery syndrome, postraumatic paraplegia.
Interventions	50 ml syringes provided by the HUG pharmacy will contain 1% ketamine or 0.9% NaCl. After induction and before start of surgery, patients will receive an intravenous bolus of 0.025 ml/kg of the study solution (corresponding to 0.25 mg/kg ketamine). Maintenance will be with a syringe driver at a rate of 0.025 ml/kg/h (corresponding to 0.25 mg/kg/h ketamine) until one hour before the end of surgery, and will then be decreased to a rate of 0.01 ml/kg/h (corresponding to 0.1 mg/kg/h ketamine) throughout the stay in the recovery room (usually 2 to 3 hours). The infusion will be stopped when the patient leaves the recovery room.
Outcomes	Primary outcome measures: 6 and 12 months effect of perioperative intravenous low-dose ketamine on chronic neuropathic pain in patients undergoing major back surgery. Secondary long-term outcome measures: short-term (during hospitalisation) effect of perioperative intravenous low-dose ketamine in patients undergoing major back surgery: tolerability and safety, opioid-sparing effect, pain intensity, morphine-related adverse effects. To study psychosocial factors that may be involved in the perception of acute and chronic postoperative pain in patients with or without chronic back pain undergoing back surgery.
Starting date	October 2007
Contact information	Study Chair: Martin Tramèr, Prof, MD, PhD. Christoph Czarnetzki, Responsable Investigator, University Hospital, Geneva
Notes	This study is ongoing, but not recruiting participants. First received on February 6, 2008. Last updated on April 3, 2012

NCT00631891

Study name	Pregabalin in Treating Pain in Women Undergoing Mastectomy or Lumpectomy
Methods	Randomized, double-blind, clinical trial
Participants	Patients (ASA I-III) undergoing unilateral modified radical mastectomy or lumpectomy with axillary node dissection. Exclusion criteria: allergy to study drugs, drug/alcohol abuse; kidney failure; concurrent use of other analgesics.
Interventions	Oral placebo or pregabalin 1-2 hours prior to surgery, at 12 hours after surgery, and then twice daily for 14 days
Outcomes	Primary outcome measures: pain scores at 3 months; PCA morphine consumption; side effects profile; and modified Brief Pain Inventory-short form
Starting date	December 2006
Contact information	Babatunde Ogunnaike, Simmons Comprehensive Cancer Center at University of Texas Southwestern Medical Center - Dallas
Notes	The recruitment status of this study is unknown because the information has not been verified recently. Verified May 2009 by National Cancer Institute (NCI). Recruitment status was: Recruiting

NCT00663962

Study name	Pregabalin and Post-thoracotomy Pain
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients (18-75; ASA I-III)undergoing elective thoracotomy (ET) or video assisted thoracotomy (VAT). Exclusion criteria: intolerance to study drugs; Contraindication to thoracic epidural placement; Renal insufficiency (serum creatinine > 1.5 x upper limit of normal); Body Mass Index > 40; surgery extending to the chest wall; alcohol abuse; chronic pain/analgesic use; History of congestive heart failure; Major psychiatric disorder; Insufficient safety data in a specific patient population; Pregnant or breastfeeding.
Interventions	Pregabalin 150mg or 300 mg or placebo administered 1 hour prior to surgery and 12 hours after surgery, then continued BID until day 7 post-op
Outcomes	Primary outcome measures: The primary outcome measure for the final study will be the incidence of CPTPS at 2 months. [Time Frame: 2, 4, and 6 months]
Starting date	April 2008
Contact information	Dr Jorge Enrique Zamora, Department of Anesthesiology, Queen's University
Notes	The recruitment status of this study is unknown because the information has not been verified recently. Verified September 2009 by Queen's University. Recruitment status was active, not recruiting

NCT00762099

Study name	Perioperative Pregabalin Use, Rehabilitation, Pain Outcomes and Anxiety Following Hip Surgery (RCT)
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: Patients (18-75), ASA I-III undergoing total hip arthroplasty. Exclusion criteria: allergy to study drugs; drug/alcohol/opioid abuse; rheumatoid arthritis; psychiatric disorders; renal failure; obesity.
Interventions	Pre-operative pregabalin 150 mg or placebo plus post-operative dose 75 mg bid or placebo
Outcomes	Movement-evoked pain scores at 6 weeks and 3 months post surgery
Starting date	May 2009
Contact information	Colin McCartney, MD. colin.mccartney@sunnybrook.ca
Notes	This study is currently recruiting participants. Verified April 2011 by Sunnybrook Health Sciences Centre

NCT00852683

Study name	The Effects of Peri-Operative Pregabalin on Post-Operative Pain Following Breast Cancer Surgery With Axillary Node Dissection: A Pilot Study
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients (18-60), ASA I-III undergoing breast surgery with axillary dissection for the treatment of breast cancer. Exclusion criteria: persons with a history of allergy to gabapentin or pregabalin, morphine, NSAIDs, acetaminophen or oxycodone; pregnancy; Body Mass Index >40; liver or renal failure; chronic opioid users (30 mg per day of morphine equivalent); gabapentin or pregabalin users within 3 months of surgery; persons with a history of drug abuse.
Interventions	Participants will receive pregabalin (75 mg BID) or placebo (sugar pills) for BID for 14 days starting 1 hour before surgery
Outcomes	Primary Outcome Measures: numeric rating pain Score at rest and with movement 24 hours after surgery. Secondary Outcome Measures: Incidence of chronic post-mastectomy pain at 3 months defined as persistent pain or discomfort not present prior to surgery and not present as a result of new or recurrent tumour growth.
Starting date	May 2008
Contact information	Peter MacDougall, MD. pcmacdou@gmail.com
Notes	This study is currently recruiting participants. Verified January 2009 by Capital District Health Authority, Canada

NCT00905437

Study name	Study To Investigate The Effectiveness Of Pregabalin For Management Of Patients Undergoing Total Hip Replacement
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients undergoing total primary or secondary hip replacement surgery performed under spinal anesthesia. Exclusion criteria: revision surgery, hip replacement secondary to trauma; history of uncontrolled chronic disease or a concurrent clinically significant illness or medical condition, which in the Investigator's opinion, would contraindicate study participation or confound interpretation of the results.
Interventions	Placebo or pregabalin 75 mg BID for 14 days
Outcomes	Primary outcome measures: O-10 Pain score on Movement obtained over postoperative Days 1-5. Secondary long-term outcome measures: Incidence of neuropathic pain as detected using the ID Pain questionnaire 3 & 6 months following the surgery.
Starting date	November 2009
Contact information	Pfizer
Notes	This study is currently recruiting participants. Verified April 2012 by Pfizer

NCT00967135

Study name	Efficacy of Perioperative Pregabalin in Reducing the Incidence of Chronic Neuropathic Pain and Postthoracotomy Syndrome.
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients aged 18 to 80 years, ASA I-III, undergoing elective thoracotomy. Exclusion criteria: contraindication to pregabalin or epidural technique; current use of opioids, NMDA receptor blockers, membrane stabilizing agents (lidocaine mesylates, flecainide) or topical coanalgesics (capsaicin cream, lidocaine patch); previous use of pregabalin or gabapentin; preexisting pain at the surgical site or any other chronic pain syndrome; creatinine clearance of less than 60 mL/min; previous thoracotomy; recent history of alcohol and/or drug abuse; known allergy to local anesthetics or hydromorphone.
Interventions	Pregabalin 150 mg bid or matching placebos during 5 days, starting the days before surgery
Outcomes	Primary outcome measures: development of neuropathic pain and intensity of pain assessed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale and Brief Pain Inventory questionnaire (BPI) at 3 months
Starting date	June 2010
Contact information	Centre hospitalier de l'Université de Montréal (CHUM)
Notes	This study has been completed. First received on August 26, 2009. Last updated on April 11, 2012

NCT01022840

Study name	The Preemptive Analgetic Potency of Low Dose S-Ketamine (Miniket)
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: adult patients (ASA I-III) scheduled for major abdominal surgery, suitable for PCA, with acceptable compliance for pain monitoring. Exclusion criteria: allergy to S-Ketamine, severe liver or kidney dysfunction, severe coronary disease, pregnancy, present or past psychotic disorders, addiction to alcohol or opioids.
Interventions	3 groups: placebo as saline solution, low dose ketamine and high dose ketamine
Outcomes	Primary Outcome Measures: postoperative opioid consumption [Time Frame: 1 year]
Starting date	February 2009
Contact information	Andreas Sandner-Kiesling, MD (andreas.sandner@medunigraz.at)
Notes	This study is currently recruiting participants. Verified February 2012 by Medical University of Graz

NCT01116583

Study name	The Effect of Gabapentin on Thoracic Epidural Analgesia Following Thoracotomy (GABATEA)
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients undergoing elective lung resection via thoracotomy, aged 18- 80 years. Exclusion criteria: Inability to answer the detailed questionnaires on pain and quality of life; Psychiatric disease (ICD-10); Severe renal impairment (se-creatinin > 110 mmol/l); chronic opioid or anticonvulsant or antidepressant user; allergy to study drugs; user of antacids 24 hours before the intake of study medication; previous ipsilateral thoracotomy; chronic pain syndrome; acute pancreatitis; history of past or current alcohol and / or illegal substance abuse; history of gastric or duodenal ulcer; gastrointestinal obstruction; pregnancy.
Interventions	Preoperative gabapentin (1200 mg) or placebos plus postoperative increasing dose of gabapentin (600 - 1200 mg) or matching placebos up to the 5th day after surgery
Outcomes	Primary outcome measures: persistent postsurgical pain at 3, 6 & 12 months after surgery by Brief Pain Inventory and The McGill Pain Questionnaire. Persistent postoperative pain is measured both on a 11-point numeric pain rating scale and on a 10 cm visual analog scale (VAS). A score >=3 is considered as moderate pain. Secondary long-term outcome measures: Health related quality of life measured at 3, 6 and 12 months.
Starting date	May 2011
Contact information	Hans K Pilegaard, MD, Chief Surgeon
Notes	This study is currently recruiting participants. Verified March 2012 by University of Aarhus

NCT01204242

Study name	IV Lidocaine for Patients Undergoing Primary Breast Cancer Surgery: Effects on Postoperative Recovery and Cancer
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: patients aged 18 to 80 years, ASA I-III, scheduled for breast cancer mastectomy. Exclusion criteria: allergy to study drugs, severe cardiovascular disease (myocardial infarction within 6 months), profoundly decreased left ventricular function (ejection fraction <40%) or high-grade arrhythmias, severe liver disease, renal impairment, or pregnancy.
Interventions	Subjects will receive lidocaine up to 1.5mg/kg intravenously plus infusion of the study medication (containing lidocaine 8 mg/ml or placebo) for up to 2 hours in the recovery room.
Outcomes	Primary Outcome Measures: opioid consumption the first week after surgery. Secondary long term Outcome Measures: chronic pain at 6 months after surgery; cancer recurrence at 5 years after surgery.
Starting date	August 2009
Contact information	Mohammed Tiouririne, MD
Notes	This study is enrolling participants by invitation only. First Received on September 15, 2010. Last Updated on August 9, 2011

NCT01243801

Study name	Prevention of Persistent Postsurgical Pain After Thoracotomy
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: adult patients submitted to thoracotomy or mini-thoracotomy expected to be extubated in the operating room Exclusion criteria: allergy or intolerance to study drugs; Chronic preoperative pain; Chronic opioid treatment; Drug addiction; Polyneuropathy; Ischemic cardiopathy; or Psychiatric disease
Interventions	Bolus of epidural or intravenous ketamine during the induction of anesthesia plus infusion of ketamine the first 2 days after surgery. Postoperative analgesia: Epidural "Patient Controlled Analgesia" with ropivacaine and fentanyl. A Placebo Group will receive epidural "Patient Controlled Analgesia" with ropivacaine and fentanyl
Outcomes	Primary outcome measures: pain scores, Neuropathic Pain Symptoms Inventory, and Catastrophism Scale at 3 months and 6 months after surgery. Change from hyperalgesia peri-incisional area at 3 months and 6 months after surgery. Hyperalgesia measured with von Frey monofilaments, electronic von frey and electric brush around the surgical incision and in a separate area (thigh). Secondary outcome measures: adverse effects: any time until 6 months.
Starting date	September 2008
Contact information	Barcelona, Spain, 08036 Contact: Beatriz Tena 0034932275400 ext 5558 btena@clinic.ub.es

NCT01243801 *(Continued)*

	Principal Investigator: Beatriz Tena, MD
Notes	This study is currently recruiting participants. Verified June 2011 by Hospital Clinic of Barcelona

NCT01296347

Study name	Low Dose Peri-operative IV Ketamine for Chronic Post-surgery Pain Prevention
Methods	Randomized, double-blind, clinical trial
Participants	Adult patients undergoing either thoracotomy or video assisted thoracic surgery. Exclusion criteria: history of previous chronic thoracic pain; neuropathic pain (whatever the site), existing at time of recruitment; pre-operative analgesic treatments with strong opioids or tricyclic antidepressants, venlafaxine, gabapentin, pregabalin, duloxetine, clonazepam or carbamazepine. Allergy to study drugs.
Interventions	Intravenous infusion of saline or ketamine running at 0.1mg/kg/hour, starting 10 minutes prior to surgery up to 96 hours in total. A loading dose of ketamine (0.1 mg per kg) will be administered.
Outcomes	Primary outcome measures: incidence of pain (0-10) at 6 weeks after surgery, brief Pain Inventory, and Leeds Assessment of Neuropathic Symptoms and Signs. Secondary long-term outcome measures: analgesic consumption at 3, 6 and 12 months. Sensory testing at 6 months & 12 months. Incidence of pain (0-10) at 3, 6 and 12 months, Brief Pain Inventory, and Leeds Assessment of Neuropathic Symptoms and Signs.
Starting date	April 2011
Contact information	Contact: Gillian M Chumbley, BSc, PhD. gillian.chumbley@imperial.nhs.uk
Notes	This study is not yet open for participant recruitment. Verified January 2011 by Imperial College Healthcare NHS Trust

NCT01359059

Study name	Pre- Versus Post-incisional Pregabalin for Postoperative Pain Attenuation and Analgesics Spare in Orthopedic Oncologic Patients
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: ASA physical status I-III adult patients who will undergo bone with or without soft tissue cancer surgery type II and III under general or epidural anesthesia. Exclusion criteria: allergy to study drugs; chronic pain; psychiatric disorders; chronic use of centrally acting drugs of any sort, pregnancy.
Interventions	Patients will receive 150 mg of pregabalin or placebo the evening before surgery and 1.5 hours before surgery and will undergo surgery under GA. A second cohort of patients will be randomized similarly but will undergo surgery under epidural analgesia. No other premedication will be administered to any patient. Post-operatively, patients who received preoperative pregabalin will be given placebo and vice versa at 2 hours after surgery. All patients will receive pregabalin 150 mg twice daily thereafter, BID postoperatively up to day 4.

NCT01359059 *(Continued)*

Outcomes	Primary outcome measures: to assess the effects of the drug administered either pre-incisionally or post-incisionally on the immediate and late setting (1- and 3 months); pain scores will be measured again 2 years after surgery.
Starting date	June 2011
Contact information	Avi A Weinbroum, Tel-Aviv Sourasky Medical Center
Notes	This study is not yet open for participant recruitment. Verified June 2011 by Tel-Aviv Sourasky Medical Center

NCT01391858

Study name	Postoperative Pain and Morphine Consumption After Mastectomy - Lyrica
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion: 80 adult women (17 - 80) undergoing mastectomy. Exclusion criteria: those with known allergy to pregabalin or morphine and those with a history of alcohol abuse, chronic pain, history of daily intake of analgesics or steroids, and patients with impaired kidney function or diabetes mellitus.
Interventions	Pregabalin 300 mg or matching placebos will be administered to each patient one to 2 hours before surgery followed by 150 mg BID during 2 weeks.
Outcomes	Primary outcome measures: opioid Requirement at 14 days; IV-PCA morphine for rescue pain management in the immediate postoperative period and oral opioids after discontinuation of IV-PCA. Secondary outcome measures: pain scores at 3 months.
Starting date	December 2006
Contact information	BABATUNDE OGUNNAIKE, MD, UT SOUTHWESTERN MEDICAL CENTER
Notes	The recruitment status of this study is unknown because the information has not been verified recently. Verified December 2009 by University of Texas Southwestern Medical Center. Recruitment status was active, not recruiting

NCT01480765

Study name	Preventing Pain After Heart Surgery
Methods	Randomized, double-blind, clinical trial
Participants	Inclusion criteria: Patients aged 18-80, undergoing sternotomy for elective cardiac surgery. Exclusion criteria: Previous sternotomy; preoperative renal failure; history of chronic non-anginal pain; chronic pain medication other than paracetamol and NSAIDs, concurrent use of oxycodone, lorazepam, or ethanol; concurrent use of any drugs for neuropathic pain (e.g. antiepileptics, antidepressants); allergy to study drugs; or pregnancy.
Interventions	Pregabalin 150mg (2 hours) or matching placebos preoperatively and bid for 10 days, followed by dose reduction to 75mg twice daily for 2 days and finally to 50 mg twice daily for 2 days Drug; a

NCT01480765 *(Continued)*	
	third group will receive a placebo controlled Ketamine infusion 0.1mg/kg/hr for 48 hours postoperatively.
Outcomes	Primary outcome measures: peri-incisional pain scores at 3 months, at rest and following 3 maximal coughs. Secondary long-term outcome measures: Neuropathic pain score at 3 months using the Short form Leeds Assessment of Neuropathic Symptoms and Signs; Quality of Life at 3 months; Preoperative and postoperative sensory test by Pressure algometry, tactile and pain detection thresholds with mechanical static stimulus using von Frey hairs and dynamic assessment of spatial and temporal summation.
Starting date	November 2011
Contact information	Sibtain Anwar, MA MB FRCA. sibtain.anwar@bartsandthelondon.nhs.uk
Notes	This study is currently recruiting participants. Verified March 2012 by Barts & The London NHS Trust

ASA: American Society of Anesthesia; BID: twice a day; NMDA: N-methyl-D-aspartate; NSAIDs: non-steroidal anti-inflammatory drugs

DATA AND ANALYSES

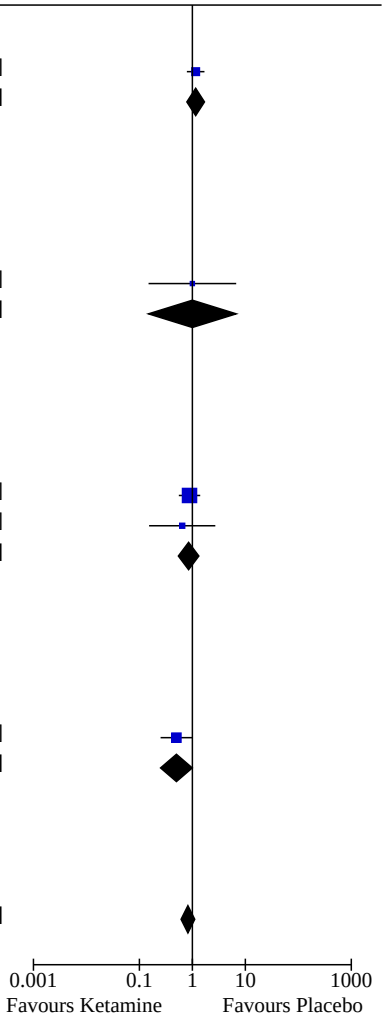
Comparison 1. Ketamine versus placebo comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Incidence of any pain at 3 months (all studies)	5	384	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.11]
1.1.1 Breast Surgery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.79, 1.69]
1.1.2 Hemorrhoidectomy	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.72]
1.1.3 Orthopedic Surgery	2	238	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.54, 1.32]
1.1.4 Thoracotomy	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.25, 1.00]
1.2 Incidence of any pain at 3 months (drug administration ≤ 24 hours)	3	249	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.69, 1.35]
1.2.1 Breast Surgery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.79, 1.69]
1.2.2 Hemorrhoidectomy	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.72]
1.2.3 Orthopedic Surgery	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.55, 1.41]
1.3 Incidence of any pain at 3 months (drug administration > 24 hours)	2	135	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 1.00]
1.3.1 Orthopedic Surgery	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.15, 2.71]
1.3.2 Thoracotomy	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.25, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Incidence of any pain at 4 months	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.48, 1.46]
1.5 Incidence of any pain at 6 months (all studies)	8	516	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.47, 0.83]
1.5.1 Abdominal and/or pelvic surgery	2	164	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.88]
1.5.2 Amputation	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.35, 1.23]
1.5.3 Breast surgery	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.47, 1.60]
1.5.4 Orthopedic surgery	3	190	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.40, 1.06]
1.5.5 Thoracotomy	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.21]
1.6 Incidence of any pain at 6 months (drug administration ≤ 24 hours)	4	318	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.36, 0.83]
1.6.1 Abdominal and/or pelvic surgery	2	164	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.88]
1.6.2 Orthopedic Surgery	2	154	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.39, 1.04]
1.7 Incidence of any pain at 6 months (drug administration > 24 hours)	4	198	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.49, 1.06]
1.7.1 Amputation	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.35, 1.23]
1.7.2 Breast Surgery	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.47, 1.60]
1.7.3 Orthopedic Surgery	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.08, 16.52]
1.7.4 Thoracotomy	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.25, 1.21]
1.8 Incidence of Moderate or severe pain at 6 months	3	259	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.95]
1.8.1 Amputation	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.32, 3.52]
1.8.2 Breast Surgery	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.18, 1.32]
1.8.3 Total hip arthroplasty	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.08, 1.02]
1.9 Incidence of any pain at 12 months	2	104	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.06, 1.15]

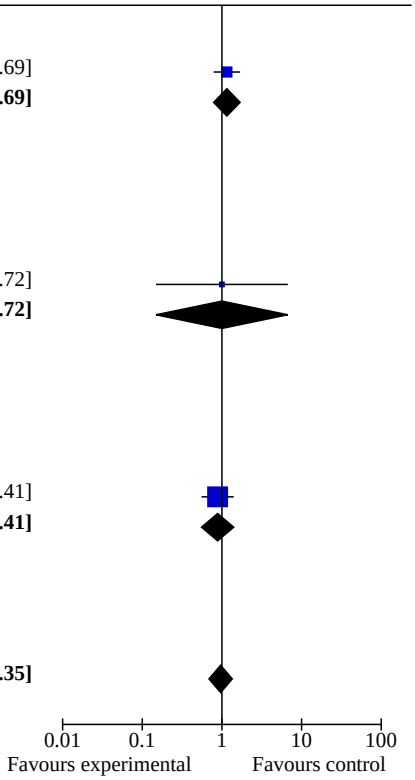
Analysis 1.1. Comparison 1: Ketamine versus placebo comparisons, Outcome 1: Incidence of any pain at 3 months (all studies)

Study or Subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Breast Surgery						
Crousier 2008	10	12	13	18	18.5%	1.15 [0.79 , 1.69]
Subtotal (95% CI)		**12**		**18**	**18.5%**	**1.15 [0.79 , 1.69]**
Total events:	10		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
1.1.2 Hemorrhoidectomy						
Spreng 2010	2	36	2	36	3.6%	1.00 [0.15 , 6.72]
Subtotal (95% CI)		**36**		**36**	**3.6%**	**1.00 [0.15 , 6.72]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.1.3 Orthopedic Surgery						
Remerand 2009	23	75	25	72	45.4%	0.88 [0.55 , 1.41]
Sveticic 2008	3	49	4	42	7.7%	0.64 [0.15 , 2.71]
Subtotal (95% CI)		**124**		**114**	**53.0%**	**0.85 [0.54 , 1.32]**
Total events:	26		29			
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.1.4 Thoracotomy						
Suzuki 2006	7	22	14	22	24.9%	0.50 [0.25 , 1.00]
Subtotal (95% CI)		**22**		**22**	**24.9%**	**0.50 [0.25 , 1.00]**
Total events:	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
Total (95% CI)		**194**		**190**	**100.0%**	**0.82 [0.61 , 1.11]**
Total events:	45		58			
Heterogeneity: Chi² = 5.25, df = 4 (P = 0.26); I² = 24%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Test for subgroup differences: Chi² = 4.49, df = 3 (P = 0.21), I² = 33.2%						



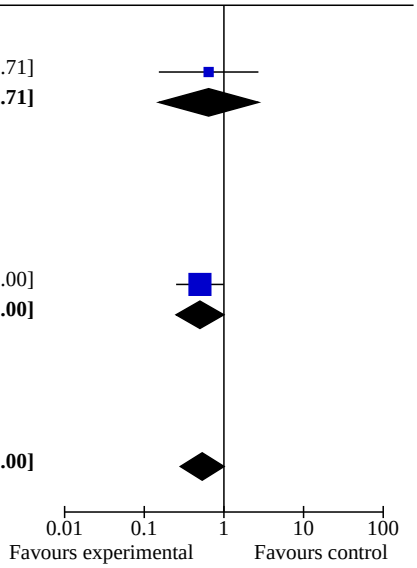
Analysis 1.2. Comparison 1: Ketamine versus placebo comparisons, Outcome 2: Incidence of any pain at 3 months (drug administration ≤ 24 hours)

Study or Subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Breast Surgery						
Crousier 2008	10	12	13	18	27.4%	1.15 [0.79 , 1.69]
Subtotal (95% CI)		**12**		**18**	**27.4%**	**1.15 [0.79 , 1.69]**
Total events:	10		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
1.2.2 Hemorrhoidectomy						
Spreng 2010	2	36	2	36	5.3%	1.00 [0.15 , 6.72]
Subtotal (95% CI)		**36**		**36**	**5.3%**	**1.00 [0.15 , 6.72]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.2.3 Orthopedic Surgery						
Remerand 2009	23	75	25	72	67.3%	0.88 [0.55 , 1.41]
Subtotal (95% CI)		**75**		**72**	**67.3%**	**0.88 [0.55 , 1.41]**
Total events:	23		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						
Total (95% CI)		**123**		**126**	**100.0%**	**0.96 [0.69 , 1.35]**
Total events:	35		40			
Heterogeneity: Chi² = 0.99, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Chi² = 0.76, df = 2 (P = 0.68), I² = 0%						



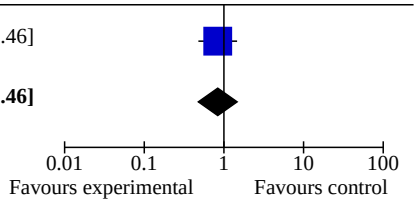
Analysis 1.3. Comparison 1: Ketamine versus placebo comparisons, Outcome 3: Incidence of any pain at 3 months (drug administration > 24 hours)

Study or Subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Orthopedic Surgery						
Sveticic 2008	3	49	4	42	23.5%	0.64 [0.15 , 2.71]
Subtotal (95% CI)		**49**		**42**	**23.5%**	**0.64 [0.15 , 2.71]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.3.2 Thoracotomy						
Suzuki 2006	7	22	14	22	76.5%	0.50 [0.25 , 1.00]
Subtotal (95% CI)		**22**		**22**	**76.5%**	**0.50 [0.25 , 1.00]**
Total events:	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
Total (95% CI)		**71**		**64**	**100.0%**	**0.53 [0.28 , 1.00]**
Total events:	10		18			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.95 (P = 0.05)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.76), I² = 0%						

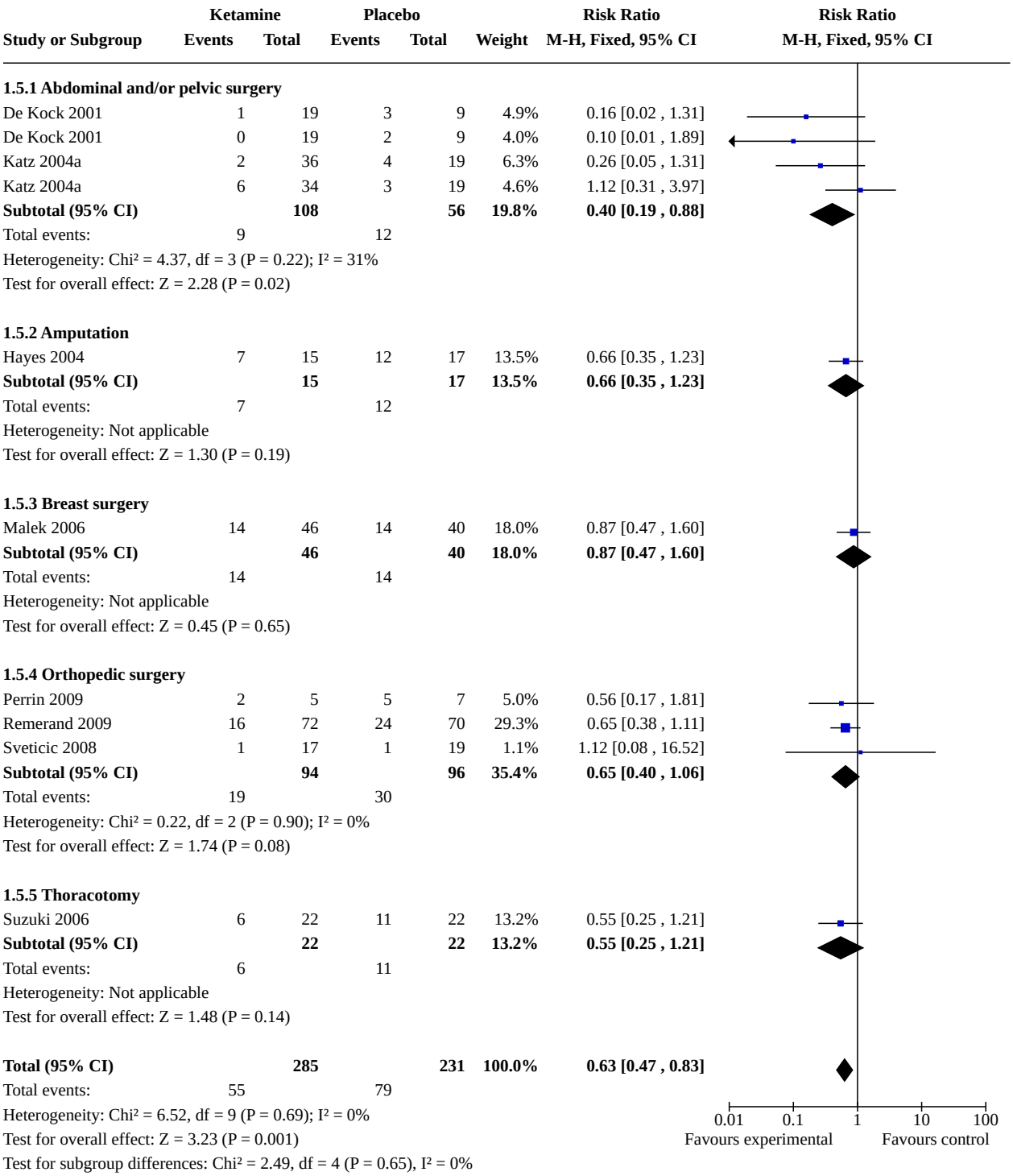


Analysis 1.4. Comparison 1: Ketamine versus placebo comparisons, Outcome 4: Incidence of any pain at 4 months

Study or Subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Duale 2009	13	34	16	35	100.0%	0.84 [0.48 , 1.46]
Total (95% CI)		**34**		**35**	**100.0%**	**0.84 [0.48 , 1.46]**
Total events:	13		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Not applicable						

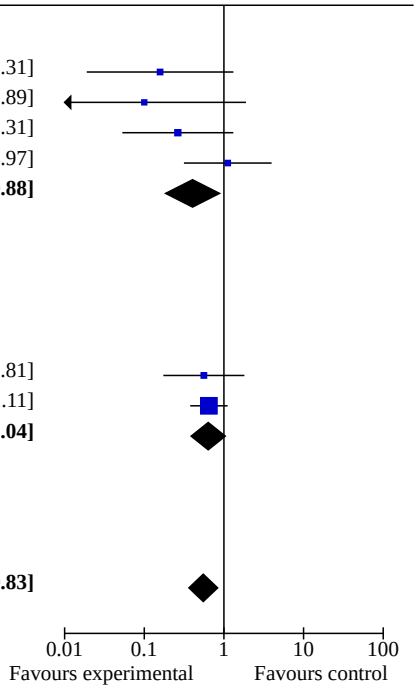


Analysis 1.5. Comparison 1: Ketamine versus placebo comparisons, Outcome 5: Incidence of any pain at 6 months (all studies)

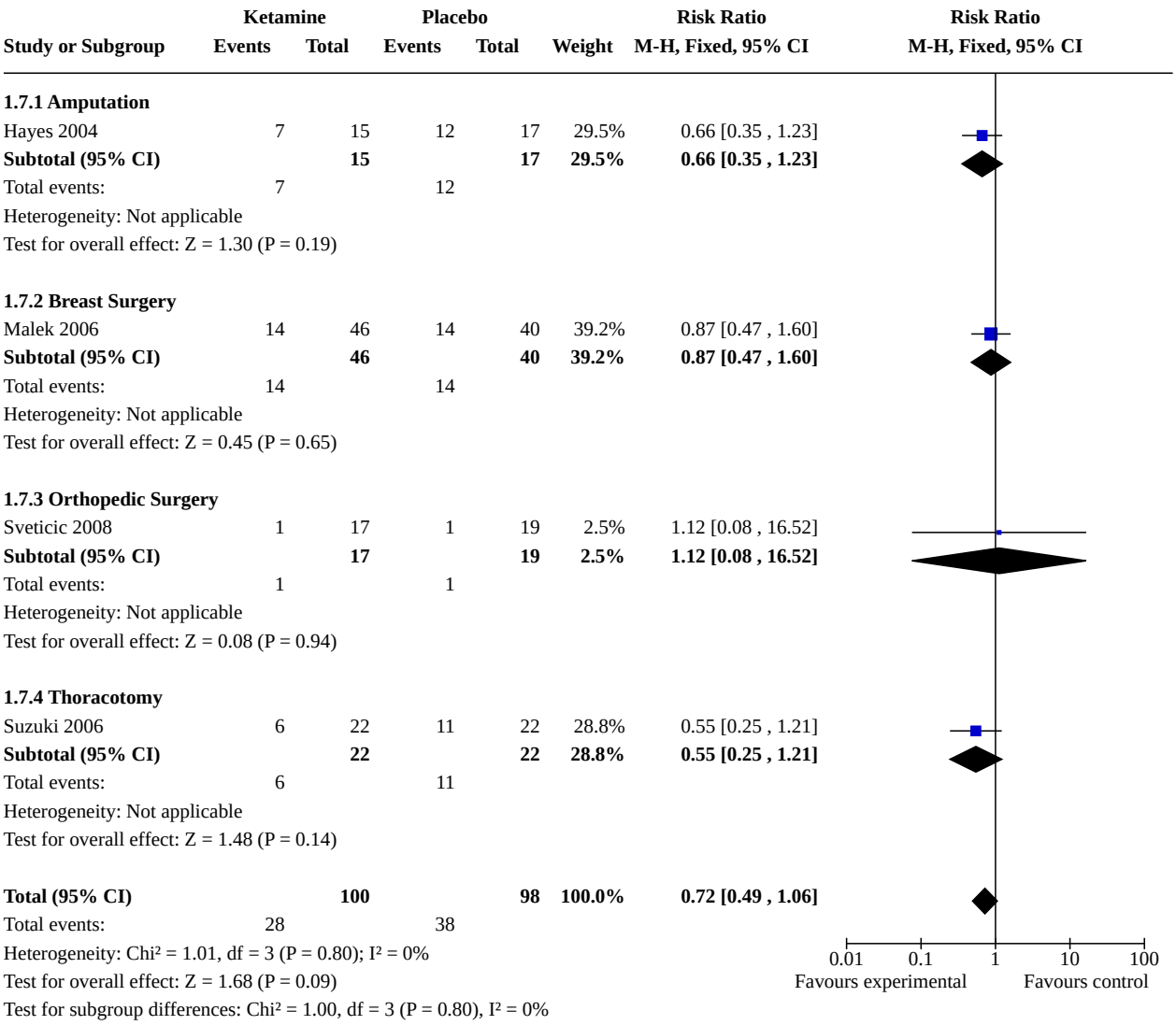


Analysis 1.6. Comparison 1: Ketamine versus placebo comparisons, Outcome 6: Incidence of any pain at 6 months (drug administration ≤ 24 hours)

Study or Subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Abdominal and/or pelvic surgery						
De Kock 2001	1	19	3	9	9.0%	0.16 [0.02 , 1.31]
De Kock 2001	0	19	2	9	7.4%	0.10 [0.01 , 1.89]
Katz 2004a	2	36	4	19	11.6%	0.26 [0.05 , 1.31]
Katz 2004a	6	34	3	19	8.6%	1.12 [0.31 , 3.97]
Subtotal (95% CI)		**108**		**56**	**36.6%**	**0.40 [0.19 , 0.88]**
Total events:	9		12			
Heterogeneity: Chi² = 4.37, df = 3 (P = 0.22); I² = 31%						
Test for overall effect: Z = 2.28 (P = 0.02)						
1.6.2 Orthopedic Surgery						
Perrin 2009	2	5	5	7	9.3%	0.56 [0.17 , 1.81]
Remerand 2009	16	72	24	70	54.1%	0.65 [0.38 , 1.11]
Subtotal (95% CI)		**77**		**77**	**63.4%**	**0.64 [0.39 , 1.04]**
Total events:	18		29			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)		**185**		**133**	**100.0%**	**0.55 [0.36 , 0.83]**
Total events:	27		41			
Heterogeneity: Chi² = 4.99, df = 5 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.82 (P = 0.005)						
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.34), I² = 0%						

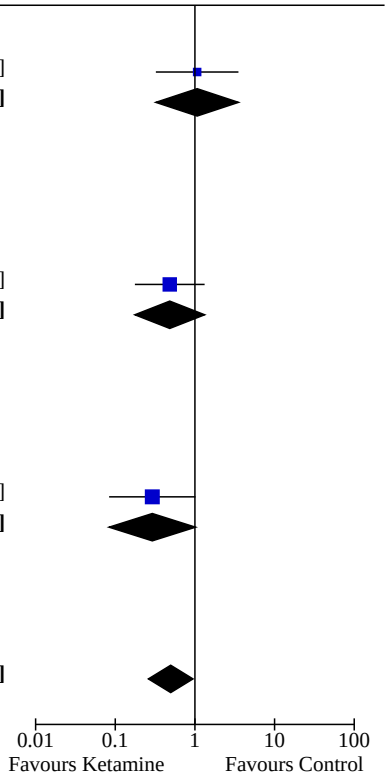


Analysis 1.7. Comparison 1: Ketamine versus placebo comparisons, Outcome 7: Incidence of any pain at 6 months (drug administration > 24 hours)



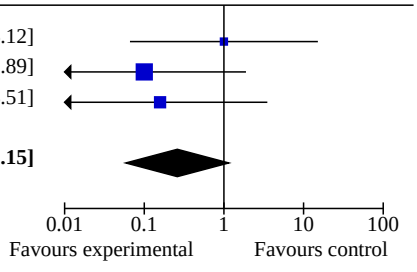
Analysis 1.8. Comparison 1: Ketamine versus placebo comparisons, Outcome 8: Incidence of Moderate or severe pain at 6 months

Study or Subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Amputation						
Hayes 2004	4	15	4	16	16.4%	1.07 [0.32 , 3.52]
Subtotal (95% CI)		**15**		**16**	**16.4%**	**1.07 [0.32 , 3.52]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.92)						
1.8.2 Breast Surgery						
Malek 2006	5	46	9	40	40.7%	0.48 [0.18 , 1.32]
Subtotal (95% CI)		**46**		**40**	**40.7%**	**0.48 [0.18 , 1.32]**
Total events:	5		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
1.8.3 Total hip arthroplasty						
Remerand 2009	3	72	10	70	42.9%	0.29 [0.08 , 1.02]
Subtotal (95% CI)		**72**		**70**	**42.9%**	**0.29 [0.08 , 1.02]**
Total events:	3		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
Total (95% CI)		**133**		**126**	**100.0%**	**0.50 [0.26 , 0.95]**
Total events:	12		23			
Heterogeneity: Chi² = 2.28, df = 2 (P = 0.32); I² = 12%						
Test for overall effect: Z = 2.13 (P = 0.03)						
Test for subgroup differences: Chi² = 2.23, df = 2 (P = 0.33), I² = 10.4%						



Analysis 1.9. Comparison 1: Ketamine versus placebo comparisons, Outcome 9: Incidence of any pain at 12 months

Study or Subgroup	Ketamine Events	Ketamine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chaparro 2010	1	25	1	25	15.7%	1.00 [0.07 , 15.12]
De Kock 2001	0	19	2	9	52.3%	0.10 [0.01 , 1.89]
De Kock 2001	0	18	1	8	32.0%	0.16 [0.01 , 3.51]
Total (95% CI)		**62**		**42**	**100.0%**	**0.26 [0.06 , 1.15]**
Total events:	1		4			
Heterogeneity: Chi² = 1.45, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.78 (P = 0.08)						
Test for subgroup differences: Not applicable						

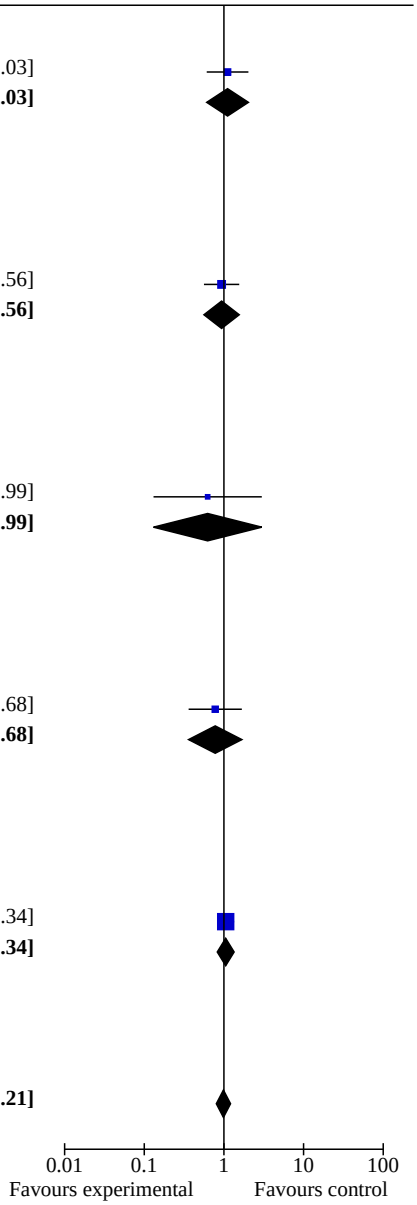


Comparison 2. Gabapentin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incidence of any pain at 3 months (all studies)	5	280	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.21]
2.1.1 Amputation (phantom limb pain)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.61, 2.03]
2.1.2 Breast Surgery	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.56, 1.56]
2.1.3 Caesarean section	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.13, 2.99]
2.1.4 Cardiac Surgery	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.36, 1.68]
2.1.5 Thoracotomy	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.83, 1.34]
2.2 Incidence of any pain at 3 months (drug administration ≤ 24 hours)	2	156	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.30]
2.2.1 Caesarean section	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.13, 2.99]
2.2.2 Thoracotomy	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.83, 1.34]
2.3 Incidence of any pain at 3 months (drug administration > 24 hours)	3	124	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.66, 1.34]
2.3.1 Amputation (phantom limb pain)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.61, 2.03]
2.3.2 Breast surgery	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.56, 1.56]
2.3.3 Cardiac surgery	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.36, 1.68]
2.4 Incidence of any pain at 6 months	2	116	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.68]
2.4.1 Amputation (phantom limb pain)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.64, 1.97]
2.4.2 Total hip arthroplasty	1	82	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.60, 1.98]
2.5 Mean Pain Score at 6 months (continuous data)	1	100	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-5.16, 3.16]

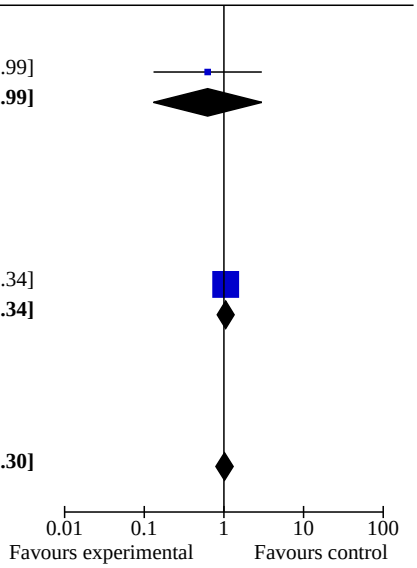
Analysis 2.1. Comparison 2: Gabapentin versus placebo, Outcome 1: Incidence of any pain at 3 months (all studies)

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Amputation (phantom limb pain)						
Nikolajsen 2006	10	18	10	20	12.6%	1.11 [0.61 , 2.03]
Subtotal (95% CI)		**18**		**20**	**12.6%**	**1.11 [0.61 , 2.03]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
2.1.2 Breast Surgery						
Fassoulaki 2002	12	22	14	24	17.8%	0.94 [0.56 , 1.56]
Subtotal (95% CI)		**22**		**24**	**17.8%**	**0.94 [0.56 , 1.56]**
Total events:	12		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
2.1.3 Caesarean section						
Moore 2011	2	16	4	20	4.7%	0.63 [0.13 , 2.99]
Subtotal (95% CI)		**16**		**20**	**4.7%**	**0.63 [0.13 , 2.99]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
2.1.4 Cardiac Surgery						
Ucak 2011	7	20	9	20	11.9%	0.78 [0.36 , 1.68]
Subtotal (95% CI)		**20**		**20**	**11.9%**	**0.78 [0.36 , 1.68]**
Total events:	7		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
2.1.5 Thoracotomy						
Kinney 2011	40	57	42	63	53.0%	1.05 [0.83 , 1.34]
Subtotal (95% CI)		**57**		**63**	**53.0%**	**1.05 [0.83 , 1.34]**
Total events:	40		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**133**		**147**	**100.0%**	**0.99 [0.80 , 1.21]**
Total events:	71		79			
Heterogeneity: Chi^2 = 1.16, df = 4 (P = 0.88); I^2 = 0%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Chi^2 = 1.10, df = 4 (P = 0.89), I^2 = 0%						



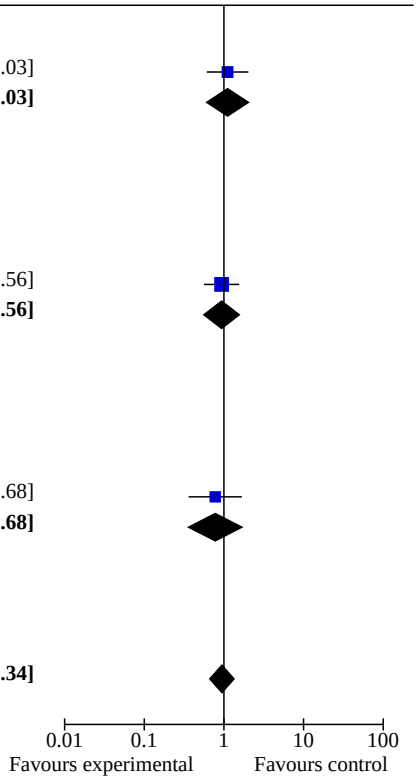
Analysis 2.2. Comparison 2: Gabapentin versus placebo, Outcome 2: Incidence of any pain at 3 months (drug administration ≤ 24 hours)

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Caesarean section						
Moore 2011	2	16	4	20	8.2%	0.63 [0.13 , 2.99]
Subtotal (95% CI)		**16**		**20**	**8.2%**	**0.63 [0.13 , 2.99]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
2.2.2 Thoracotomy						
Kinney 2011	40	57	42	63	91.8%	1.05 [0.83 , 1.34]
Subtotal (95% CI)		**57**		**63**	**91.8%**	**1.05 [0.83 , 1.34]**
Total events:	40		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**73**		**83**	**100.0%**	**1.02 [0.79 , 1.30]**
Total events:	42		46			
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%						



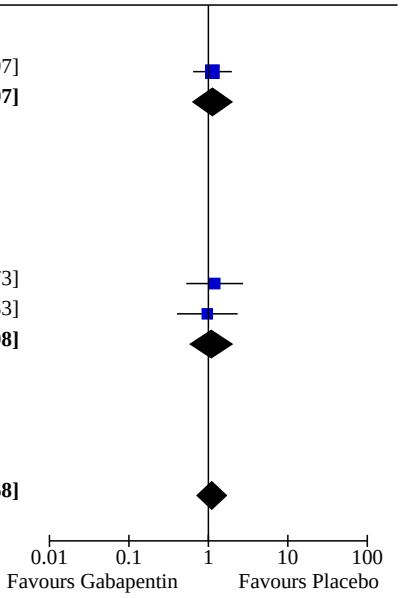
Analysis 2.3. Comparison 2: Gabapentin versus placebo, Outcome 3: Incidence of any pain at 3 months (drug administration > 24 hours)

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Amputation (phantom limb pain)						
Nikolajsen 2006	10	18	10	20	29.7%	1.11 [0.61 , 2.03]
Subtotal (95% CI)		**18**		**20**	**29.7%**	**1.11 [0.61 , 2.03]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
2.3.2 Breast surgery						
Fassoulaki 2002	12	22	14	24	42.0%	0.94 [0.56 , 1.56]
Subtotal (95% CI)		**22**		**24**	**42.0%**	**0.94 [0.56 , 1.56]**
Total events:	12		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
2.3.3 Cardiac surgery						
Ucak 2011	7	20	9	20	28.2%	0.78 [0.36 , 1.68]
Subtotal (95% CI)		**20**		**20**	**28.2%**	**0.78 [0.36 , 1.68]**
Total events:	7		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**60**		**64**	**100.0%**	**0.94 [0.66 , 1.34]**
Total events:	29		33			
Heterogeneity: Chi² = 0.53, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Chi² = 0.52, df = 2 (P = 0.77), I² = 0%						



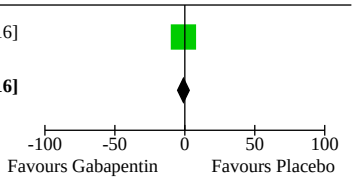
Analysis 2.4. Comparison 2: Gabapentin versus placebo, Outcome 4: Incidence of any pain at 6 months

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Amputation (phantom limb pain)						
Nikolajsen 2006	10	16	10	18	41.7%	1.13 [0.64 , 1.97]
Subtotal (95% CI)		**16**		**18**	**41.7%**	**1.13 [0.64 , 1.97]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
2.4.2 Total hip arthroplasty						
Clarke 2009	12	28	5	14	29.5%	1.20 [0.53 , 2.73]
Clarke 2009	9	26	5	14	28.8%	0.97 [0.40 , 2.33]
Subtotal (95% CI)		**54**		**28**	**58.3%**	**1.09 [0.60 , 1.98]**
Total events:	21		10			
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**70**		**46**	**100.0%**	**1.10 [0.72 , 1.68]**
Total events:	31		20			
Heterogeneity: Chi² = 0.13, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%						



Analysis 2.5. Comparison 2: Gabapentin versus placebo, Outcome 5: Mean Pain Score at 6 months (continuous data)

Study or Subgroup	Gabapentin Mean	Gabapentin SD	Gabapentin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Amr 2010	21	12	50	22	9	50	100.0%	-1.00 [-5.16 , 3.16]
Total (95% CI)			**50**			**50**	**100.0%**	**-1.00 [-5.16 , 3.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
Test for subgroup differences: Not applicable								

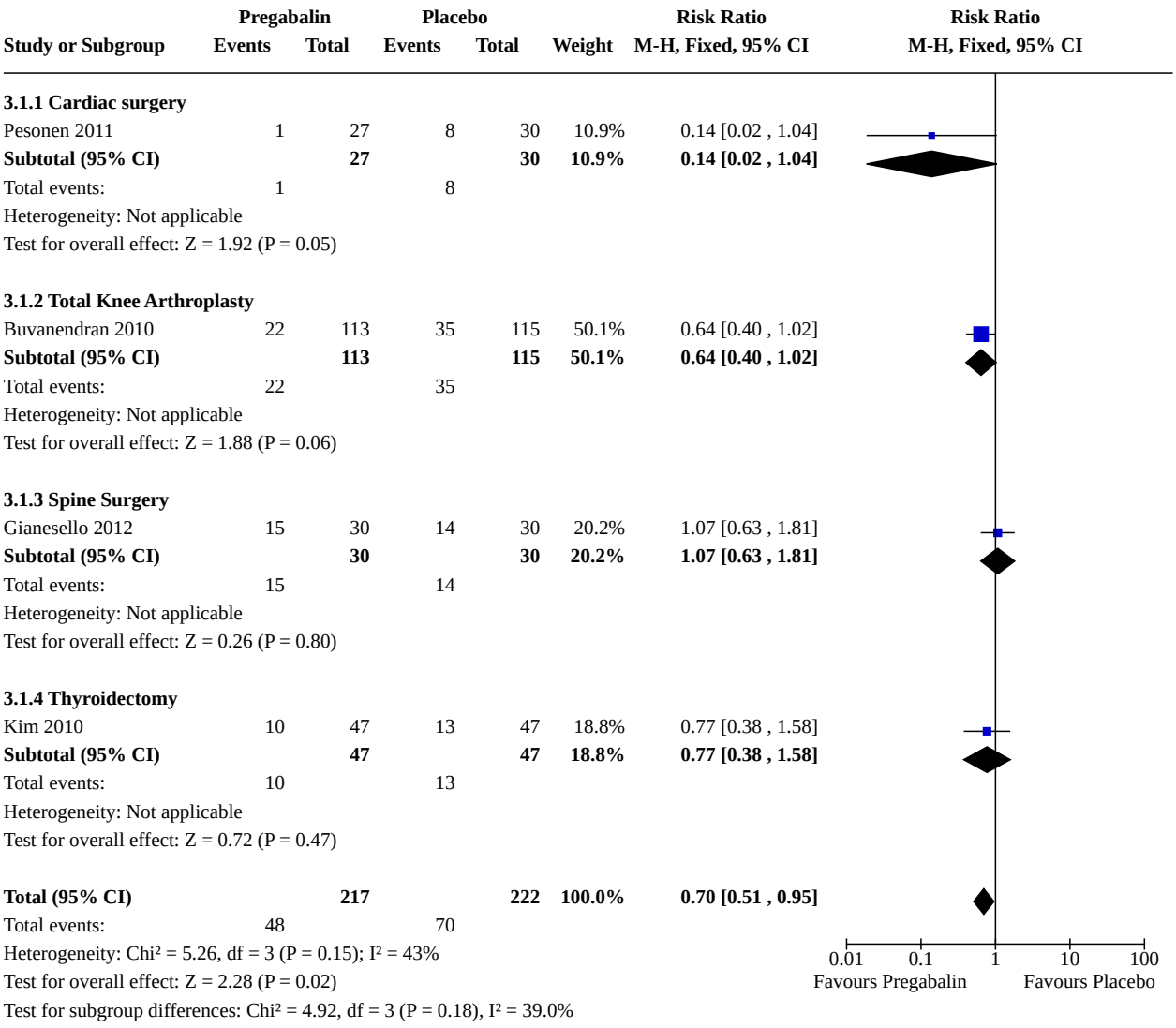


Comparison 3. Pregabalin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Incidence of any pain at 3 months follow up (all studies)	4	439	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.51, 0.95]
3.1.1 Cardiac surgery	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.04]
3.1.2 Total Knee Arthroplasty	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.40, 1.02]
3.1.3 Spine Surgery	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.63, 1.81]
3.1.4 Thyroidectomy	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.38, 1.58]

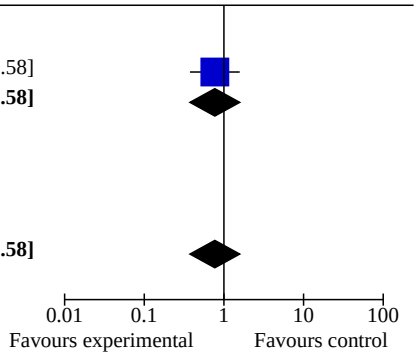
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Incidence of any pain at 3 months (drug administration ≤ 24 hours)	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.38, 1.58]
3.2.1 Thyroidectomy	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.38, 1.58]
3.3 Incidence of any pain at 3 months (drug administration > 24 hours)	3	345	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.48, 0.96]
3.3.1 Cardiac Surgery	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.04]
3.3.2 Total knee arthroplasty	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.40, 1.02]
3.3.3 Spine surgery	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.63, 1.81]
3.4 Incidence of any pain at 6 months	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.30, 0.93]
3.4.1 Total Knee Arthroplasty	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.30, 0.93]
3.5 Incidence of moderate to severe pain at 3 months	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.20, 0.94]
3.5.1 Total Knee Arthroplasty	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.20, 0.94]
3.6 Incidence of moderate to severe pain at 6 months	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.80]
3.6.1 Total knee arthroplasty	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.80]
3.7 Incidence of any pain at 12 months follow up	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.23, 1.69]
3.7.1 Major spinal surgery	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.23, 1.69]

Analysis 3.1. Comparison 3: Pregabalin versus placebo, Outcome 1: Incidence of any pain at 3 months follow up (all studies)



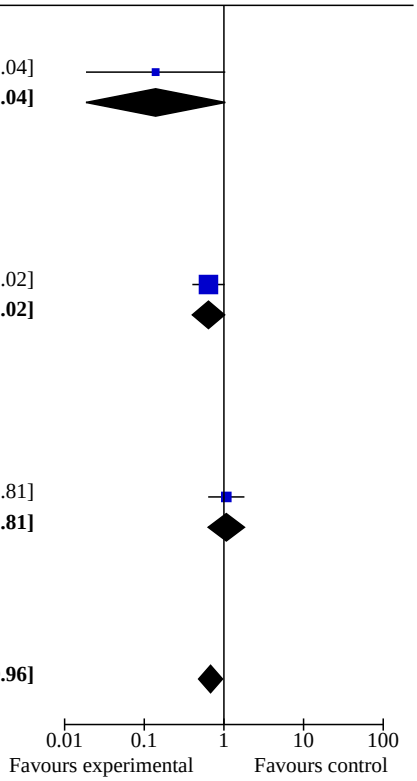
Analysis 3.2. Comparison 3: Pregabalin versus placebo, Outcome 2: Incidence of any pain at 3 months (drug administration ≤ 24 hours)

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Thyroidectomy						
Kim 2010	10	47	13	47	100.0%	0.77 [0.38 , 1.58]
Subtotal (95% CI)		**47**		**47**	**100.0%**	**0.77 [0.38 , 1.58]**
Total events:	10		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Total (95% CI)		**47**		**47**	**100.0%**	**0.77 [0.38 , 1.58]**
Total events:	10		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: Not applicable						



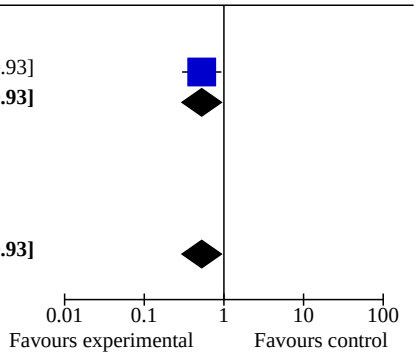
Analysis 3.3. Comparison 3: Pregabalin versus placebo, Outcome 3: Incidence of any pain at 3 months (drug administration > 24 hours)

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Cardiac Surgery						
Pesonen 2011	1	27	8	30	13.5%	0.14 [0.02 , 1.04]
Subtotal (95% CI)		**27**		**30**	**13.5%**	**0.14 [0.02 , 1.04]**
Total events:	1		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.05)						
3.3.2 Total knee arthroplasty						
Buvanendran 2010	22	113	35	115	61.7%	0.64 [0.40 , 1.02]
Subtotal (95% CI)		**113**		**115**	**61.7%**	**0.64 [0.40 , 1.02]**
Total events:	22		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						
3.3.3 Spine surgery						
Gianesello 2012	15	30	14	30	24.9%	1.07 [0.63 , 1.81]
Subtotal (95% CI)		**30**		**30**	**24.9%**	**1.07 [0.63 , 1.81]**
Total events:	15		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
Total (95% CI)		**170**		**175**	**100.0%**	**0.68 [0.48 , 0.96]**
Total events:	38		57			
Heterogeneity: $Chi^2 = 5.36$, df = 2 (P = 0.07); $I^2 = 63\%$						
Test for overall effect: Z = 2.19 (P = 0.03)						
Test for subgroup differences: $Chi^2 = 4.92$, df = 2 (P = 0.09), $I^2 = 59.3\%$						



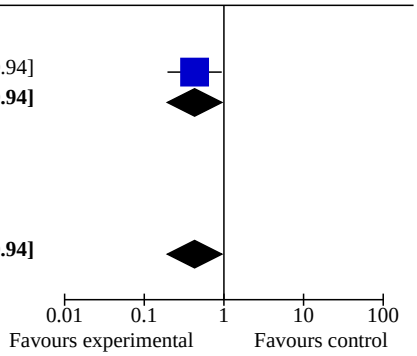
Analysis 3.4. Comparison 3: Pregabalin versus placebo, Outcome 4: Incidence of any pain at 6 months

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Total Knee Arthroplasty						
Buvanendran 2010	15	113	29	115	100.0%	0.53 [0.30 , 0.93]
Subtotal (95% CI)		**113**		**115**	**100.0%**	**0.53 [0.30 , 0.93]**
Total events:	15		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
Total (95% CI)		**113**		**115**	**100.0%**	**0.53 [0.30 , 0.93]**
Total events:	15		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
Test for subgroup differences: Not applicable						



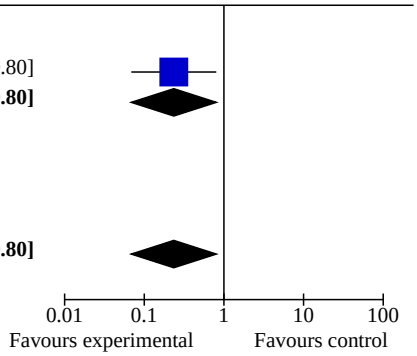
Analysis 3.5. Comparison 3: Pregabalin versus placebo, Outcome 5: Incidence of moderate to severe pain at 3 months

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Total Knee Arthroplasty						
Buvanendran 2010	8	113	19	115	100.0%	0.43 [0.20 , 0.94]
Subtotal (95% CI)		**113**		**115**	**100.0%**	**0.43 [0.20 , 0.94]**
Total events:	8		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						
Total (95% CI)		**113**		**115**	**100.0%**	**0.43 [0.20 , 0.94]**
Total events:	8		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.12 (P = 0.03)						
Test for subgroup differences: Not applicable						



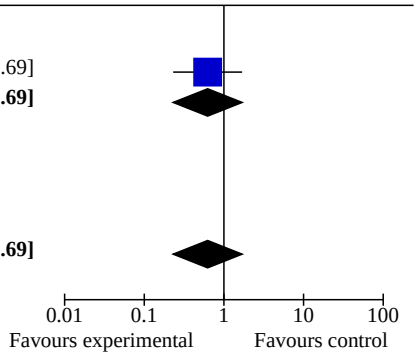
Analysis 3.6. Comparison 3: Pregabalin versus placebo, Outcome 6: Incidence of moderate to severe pain at 6 months

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 Total knee arthroplasty						
Buvanendran 2010	3	113	13	115	100.0%	0.23 [0.07 , 0.80]
Subtotal (95% CI)		**113**		**115**	**100.0%**	**0.23 [0.07 , 0.80]**
Total events:	3		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.31 (P = 0.02)						
Total (95% CI)		**113**		**115**	**100.0%**	**0.23 [0.07 , 0.80]**
Total events:	3		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.31 (P = 0.02)						
Test for subgroup differences: Not applicable						



Analysis 3.7. Comparison 3: Pregabalin versus placebo, Outcome 7: Incidence of any pain at 12 months follow up

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.7.1 Major spinal surgery						
Gianesello 2012	5	30	8	30	100.0%	0.63 [0.23 , 1.69]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.63 [0.23 , 1.69]**
Total events:	5		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)		**30**		**30**	**100.0%**	**0.63 [0.23 , 1.69]**
Total events:	5		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Not applicable						



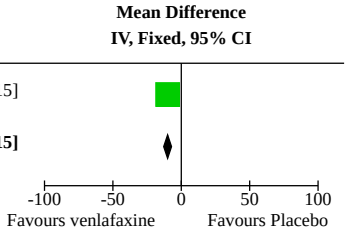
Comparison 4. Venlafaxine versus placebo comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Mean Pain Score at 6 months (continuous data)	1	100	Mean Difference (IV, Fixed, 95% CI)	-10.00 [-12.85, -7.15]

Analysis 4.1. Comparison 4: Venlafaxine versus placebo comparisons, Outcome 1: Mean Pain Score at 6 months (continuous data)

Study or Subgroup	Venlafaxine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Amr 2010	12	5	50	22	9	50	100.0%	-10.00 [-12.85 , -7.15]
Total (95% CI)			**50**			**50**	**100.0%**	**-10.00 [-12.85 , -7.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.87 (P < 0.00001)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Ketamine trials

Study ID	Surgery	Preoperative Dose (µg/kg)	Intraoperative Dose (µg/kg/h)	Postoperative Dose (µg/kg/h)	Cumulative dose (µg/kg)
Chaparro 2010	Breast surgery	420	200	none	420 + (200 x 2h) = 820*
Crousier 2008	Breast surgery	500	250	none	500 + (250 x 1.63h) = 908*
De Kock 2001	Rectal carcinoma resection	250	125	none	250 + (125 X 4.3h) = 772*
De Kock 2001	Rectal carcinoma resection	500	250	none	500 + (250 X 4.38h) = 1,595*
Duale 2009	Thoracotomy	1000	1000	1000 for 24h	3,000*
Dullenkopf 2009	Orthopedic surgery	150	none	none	150
Dullenkopf 2009	Orthopedic surgery	500	none	none	500
Hayes 2004	Amputation	500	150 for 72h		11,300
Katz 2004a	Radical prostatectomy	200	175 in 70 minutes	none	375
Katz 2004a	Radical prostatectomy	None	200 + 175 in 70 minutes	none	375
Malek 2006	Breast surgery	None	1,000/day for 48 hours		2,000
Perrin 2009	Total knee arthroplasty	500	240	none	500 + (4x125.4)= 1,001.6*
Remerand 2009	Total hip arthroplasty	500	120 for 24h		3,380*
Sen 2009a	Hysterectomy	300	50	none	300 + (50 x 1.25h)= 362.5*
Spreng 2010	Hemorrhoidectomy	350	300	none	350+ (300 x 0.33)= 451.5*

Table 1. Ketamine trials *(Continued)*

Suzuki 2006	Thoracotomy	none	50 for 72h		3,600*
Sveticic 2008	Orthopedic surgery	none	none	1.5 mg**	1,198***

*Calculation based on reported anesthesia duration.
** 1.5 mg of ketamine per each PCA opioid bolus.
***Calculation based on ketamine consumption and timing of administration.

Table 2. Gabapentin trials

Study ID	Surgery	Preoperative Dose (mg)	Postoperative Dose (mg/day)	Cumulative Dose (mg)	Cumulative Days
Amr 2010	Breast surgery	300	300	3,000	10
Brogly 2008	Thyroidectomy	1,200	none	1,200	single dose
Clarke 2009	Total hip arthroplasty	600	none	600	single dose
Clarke 2009	Total hip arthroplasty	none	600	600	single dose
Fassoulaki 2002	Breast surgery	800	1200	12,000	10
Kinney 2011	Thoracotomy	600	none	600	single dose
Moore 2011	Caesarean	600	none	600	single dose
Nikolajsen 2006	Amputation	None	300 to 2,400	75,600	30
Sen 2009a	Hysterectomy	1,200	none	1,200	single dose
Sen 2009	Inguinal herniorrhaphy	1,200	none	1,200	single dose
Ucak 2011	Cardiac surgery	1,200	1,200	3,600	2

Table 3. Pregabalin trials

Study ID	Surgery	Preoperative Dose (mg)	Postoperative Dose (mg/day)	Cumulative Dose (mg)	Cumulative Days
Burke 2010	Spine surgery	300	300	600	1
Buvanendran 2010	Total knee arthroplasty	300	300 to 100	3,800	14
Gianesello 2012	Spine surgery	300	300	900	2
Kim 2010	Thyroidectomy	150	150	300	1
Pesonen 2011	Cardiac surgery	150	150	750	5

Table 4. Other drugs

Study ID	Drug	Surgery	Preoperative Dose (mg)	Postoperative Dose (mg/day)	Cumulative Dose (mg)	Cumulative Days
Amr 2010	Venlafaxine	Mastectomy	37.5	37.5	375	10 days
Bergeron 2009	Dexamethasone	Hip arthroplasty	40	none	40	Single dose
Romundstad 2006	Methyl-prednisolone	Breast augmentation	125 mg	none	125	Single dose
Weis 2006	Hydrocortisone	Cardiac surgery	100	240 to 30	550	4 days
Chan 2011	Nitrous oxide	Numerous	Intraoperative 70%		N.A.	Intraoperative
Eisenberg 2007;	Amantadine	Mastectomy	100	200	2,800	14 days
Ilkjaer 2000	Dextro-methorphan	Hysterectomy	750	none	750	Single dose
Schley 2007	Memantine	Amputation	none	10 to 40	630	28 days
Grigoras 2012	Lidocaine	Breast surgery	Bolus 1.5 mg/kg + 1.5 mg/kg/hour up to the first hour after surgery.			
Fassoulaki 2001	Mexiletine	Mastectomy	200	400	2,400	6 days
Fassoulaki 2002	Mexiletine	Breast surgery	400	600	6,000	10 days
Fransen 2006	Ibuprofen	Hip arthroplasty	None	1,200	16,800	14 days
Lakdja 1997	Ibuprofen	Mastectomy	400	1,600	2,000	2 days
Romundstad 2006	Parecoxib	Breast augmentation	40 mg	none	40 mg	Single dose
Karanikolas 2011	Fentanyl	Amputation	58.3 mcg/h	54.5 mcg/h	Variable	2 days

APPENDICES

Appendix 1. Search strategy

The following search strategy was developed for MEDLINE (Ovid) and was adapted for the other databases to be searched

1. Pain, Postoperative/
2. (postoperative adj6 pain*) or (post-operative adj6 pain*) or post-operative-pain*
3. (post-operative adj6 analgesi*) or (postoperative adj6 analgesi*)
4. (post-surgical adj6 pain*) or (post surgical adj6 pain*) or (post-surgery adj6 pain*) or (post adj surg* adj pain*)
5. (post* adj pain*) or pain relief after or pain following surg*
6. (posttreatment adj6 pain*) or (pain control after adj6 surg*) or ((post-extraction or postextraction or post-surg*) and (pain* or discomfort))
7. (posttreatment adj6 pain*) or (pain control after adj6 surg*) or ((post-extraction or postextraction or post-surg*) and (pain* or discomfort))
8. (analgesi* adj6 postoperat*) or (analgesi* adj6 post-operat*) or (pain* adj6 after surg*) or (pain* adj6 after operat*) or (analgesi* adj6 after operat*)

9. (pain* or analgesi*) adj6 ("follow* operat*" or "follow* surg*")
10. mastectomy or postmastectomy or post-mastectomy or hernia or herniorrhaphy
11. amputat* or thoracotomy or pneumonectomy or lobectomy or sternotomy
12. #10 or #11
13. pain* or discomfort or analgesi*
14. #12 and #13
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 14
16. chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or long-lasting or phantom
17. 15 and 16

The search above was combined with the following trial design search filter which has been developed for MEDLINE.

Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Animals.sh. not (humans.sh. and animals.sh.)
10. 8 not 9

WHAT'S NEW

Date	Event	Description
23 June 2021	Amended	See Published notes.

HISTORY

Protocol first published: Issue 1, 2010
Review first published: Issue 7, 2013

Date	Event	Description
7 June 2017	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

IG, RAM, and PW served as content experts. Development of the protocol and search strategy, search for, and procurement of, studies were done by IG, SS and LC. Studies to be included were selected by SS and LC with IG as arbiter, and data extraction by LC and IG. Data entry into RevMan and subsequent analyses were done by LC. Analysis interpretation was done by LC, IG, RAM and PW. The final review was drafted by LC and IG. Both LC and IG will be responsible for the update of the final review.

DECLARATIONS OF INTEREST

IG and RAM have consulted for various pharmaceutical companies. IG and RAM have received lecture fees from pharmaceutical companies that market analgesics and other healthcare interventions. IG, RAM, and PW have received research support from charities, government and industry sources at various times, but no such support was received for this work.

SOURCES OF SUPPORT

Internal sources

- UK Cochrane Centre, UK

  Sabbatical residence for IG

External sources

- Queen's University, Canada

  Academic sabbatical stipend for IG
- Royal College of Physicians and Surgeons of Canada, Canada

  Travelling fellowship for IG

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Not applicable

NOTES

Assessed for updating in 2017

We performed a full search in May 2017 but we did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

2021 statement

This review has been updated and published elsewhere, with no change to the conclusions (Carley ME et al; Pharmacotherapy for the Prevention of Chronic Pain after Surgery in Adults: An Updated Systematic Review and Meta-analysis. *Anesthesiology* Newly Published on June 14, 2021. doi: https://doi.org/10.1097/ALN.0000000000003837). This Cochrane Review has therefore now been stabilised following discussion with the authors and editors. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Amines [therapeutic use]; Analgesics [*therapeutic use]; Chronic Pain [*prevention & control]; Cyclohexanecarboxylic Acids [therapeutic use]; Gabapentin; gamma-Aminobutyric Acid [analogs & derivatives] [therapeutic use]; Ibuprofen [therapeutic use]; Ketamine [therapeutic use]; Mexiletine [therapeutic use]; Pain, Postoperative [*prevention & control]; Pregabalin; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male