

# **Intravenous lidocaine for chronic pain: A systematic review**

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## External sources

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# Abstract

## Background

Chronic pain is common in Canada and is associated with a major social and economic burden. Intravenous (IV) lidocaine is potentially beneficial for chronic pain, however its efficacy, particularly over the longer-term, is unknown.

## Objectives

To assess the short- and long-term efficacy of IV lidocaine over placebo and other analgesics in relieving chronic pain.

## Search methods

We searched EBM Reviews (2<sup>nd</sup> Quarter 2009), which included the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effects (DARE). We also accessed EBM Reviews (3<sup>rd</sup> Quarter 2009) to search the Cochrane Methodology Register (CMR), Health Technology Assessment (HTA) database, and NHS Economic Evaluation Database (NHSEED). Other electronic databases that were searched included the ACP Journal Club database (January 1991 to June 2009), BIOSIS Previews (January 1969 to December 2008), EMBASE (January 1980 to 2009 Week 27) and MEDLINE (January 1950 to July 2, 2009). Reference lists of original articles, meta-analyses and narrative reviews on IV lidocaine for chronic pain were hand searched.

## Selection criteria

Randomized placebo-controlled or active treatment-controlled trials with IV lidocaine were analyzed.

## Data collection and analysis

Two authors independently screened titles and abstracts of electronically retrieved citations. One author completed the full text screening and then extracted and analyzed the data in duplicate iterations. Effects were summarized mainly using weighted mean differences (WMDs) for continuous data, and odds ratios (ORs) for dichotomous data. Pooled estimates from fixed effects models were used when heterogeneity accounted for less than 50% of the variability between individual effect estimates within a study pool (as assessed using the  $I^2$  statistic). Otherwise, random effects models were used.

## Results

Twenty relevant randomized controlled trials involving a total of 362 independent patients were included. Only two trials used a parallel design. Overall, there was strong evidence for an association between IV lidocaine and pain reduction on a continuous scale in comparison to placebo on the same day of treatment (fixed effects WMD: -10.56 mm; 95% CI: -14.54 to -6.59 mm;  $P < 0.0001$ ), and moderate evidence of no benefit over placebo after 24 hours (fixed effects WMD: -3.35 mm; 95% CI: -11.69 to 4.99 mm;  $P = 0.43$ ). These findings were generally robust across different effect measures. Dichotomous measures of clinically significant pain relief showed an overall benefit in favour of lidocaine over placebo during the first week post-treatment (fixed effects OR: 4.29; 95% CI: 2.09 to 8.80;  $P < 0.0001$ ), however no benefit was observed after one week (fixed effects OR: 1.38; 95% CI: 0.45 to 4.26;  $P = 0.57$ ). There was strong evidence that IV lidocaine was comparable to other IV analgesics on the day of treatment (random effects WMD: 3.79 mm; 95% CI: -6.87 to 14.46 mm;  $P = 0.49$ ) as well as at five days post-treatment (random effects WMD: 0.92 mm; 95% CI: -9.59 to 11.44 mm;  $P = 0.86$ ). On the other hand, there was moderate evidence that IV lidocaine was significantly inferior to regional sympathetic blockade at one year (random effects WMD: 28 mm; 95% CI: 20 to 36 mm).

## Authors' conclusions

IV lidocaine is efficacious for very temporary relief of chronic pain, but no more efficacious than other analgesics. There is a dearth of studies on the benefit of IV lidocaine beyond 24 hours post-treatment. Based on a very small number of studies employing follow-up beyond 24 hours, there is weak to moderate evidence that IV lidocaine has a sustained benefit for a few days after the infusion, but that this benefit disappears by 18 days after treatment. There is moderate-to-strong evidence that IV lidocaine is significantly inferior to sympathetic regional blockade at 3 months and at one year of follow-up. Future trials should employ parallel study designs to assess the efficacy of IV lidocaine over clinically important time periods.

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# Plain language summary

## **Intravenous lidocaine for chronic pain: a systematic review**

Intravenous lidocaine has been shown to relieve chronic pain in individual studies; however it is not clear how consistent this benefit is across multiple studies and over longer-term follow-up. Two earlier quantitative reviews on lidocaine and its oral analogs have been published, only one of which discussed the effect of lidocaine before and after 24 hours' follow-up. The current review was performed as an update to earlier reviews, but with the objective of assessing IV lidocaine exclusively and its potential longer-term effects. After a review of all relevant randomized controlled trials, it was found that IV lidocaine was clearly superior to placebo only within the first 24 hours of follow-up, probably superior to placebo after five days, but no better than placebo at seven to 18 days. Furthermore, IV lidocaine was no better than other analgesics prior to or after 24 hours post-treatment.

# Background

## Description of the condition

Chronic pain is generally defined as pain experienced for longer than three to six months' duration (Moore 2009). In contrast to acute pain, which is usually a well-localized symptom and which generally resolves during the early stages of tissue healing, chronic pain persists beyond the normal healing phase following an injury (Apkarian 2009). Clinically, the end of the 'normal healing phase' can be difficult to determine as this can vary with the type of tissue involved, the injured body site and the extent of tissue destruction (Kerssens 2002). Therefore, operational definitions of chronic pain invariably rely on specifying a given duration of persistent pain. For the current review, we define chronic pain as pain that is experienced for a minimum of three months.

## Description of the intervention

IV lidocaine can be administered in an inpatient or outpatient setting. Patients can be either recumbent or seated during the procedure. At the beginning of the treatment, an IV is started and typically monitored by a nurse. Infusion of a sub-anaesthetic dose of lidocaine is then initiated. Optionally, this may be preceded by a bolus infusion to achieve desired blood levels sooner. Otherwise, anywhere from 1 mg/kg to 6 mg/kg body weight of lidocaine may be infused in normal saline over approximately 30 minutes to two hours. Patients generally remain in the infusion area for a brief period of time after the infusion is completed and are then transferred to a recovery area for an additional brief monitoring period. In many studies, treatment consists of a single infusion, however in one trial patients were treated daily for 15 consecutive days (Catala 1994).

## How the intervention might work

Most studies of IV lidocaine have been conducted on patients with chronic neuropathic pain. Neuropathic pain may be attributable to primary afferent nociceptive or non-nociceptive stimuli, or to spontaneous ectopic discharges without activation of peripheral nociceptors (Tremont-Lukats 2005; Devor 1991; Mao 2000). Cell membranes of injured peripheral nerves can exhibit an increased density in sodium channels and

produce persistent spontaneous discharges that maintain a central hyperexcitable state (Tremont-Lukats 2005; Cepeda 2002). Ectopic discharges can subsequently be initiated along injured nerves, in dorsal root ganglia, and in peripheral neuromata (Tremont-Lukats 2005; Kajander, Abdi 1998; Chabal 1989; Stebbing 1994; Wall 1974).

As noted by others (Tremont-Lukats 2005), early case reports originally described the use of IV lidocaine or procaine to relieve cancer and postoperative pain (Tremont-Lukats 2005; Bartlett 1961; Keats 1951). Later, experimental studies indicated that lidocaine produced analgesia by blocking peripheral and central sodium ion gate channels, including those residing within the spinal dorsal horn (Tremont-Lukats 2005; Woolf 1985), and that if given intravenously could alleviate deafferentation pain or central pain (Boas 1982).

Studies have also suggested that the inhibition of neuronal ectopic discharges is only one of several mechanisms by which lidocaine exerts its antinociceptive action (Nagy 1996). Animal studies have shown that lidocaine is able to inhibit aberrant electrical discharges in peripheral neuromata as well as in dorsal root ganglia at concentrations well below those necessary to block nerve conduction (Tremont-Lukats 2005; Abdi 1998; Chabal 1989; Devor 1992; Keats 1951; Omana-Zapata 1997; Sotgui 1994) It has also been hypothesized that the pain relief from IV lidocaine is unlikely to be a conventional pharmacologic effect of lidocaine as the half-life of the drug is only 120 minutes (Benowitz 1978; Kastrup 1987), yet its duration of effect has anecdotally been observed to be much longer (Atkinson 1982; Boas 1982; Gilbert 1951; Kastrup 1987).

### **Why it is important to do this review**

Regular requests for authorization of intravenous lidocaine for chronic pain have been made to WorkSafeBC in recent years, however the efficacy and effectiveness of IV lidocaine remains unclear. To date, three existing systematic reviews on the efficacy of systemic lidocaine for pain reduction have been published (Kaslo 1998; Tremont-Lukats 2005; Challapalli 2005), only two of which have included a pooled estimate of the benefit of IV lidocaine across multiple studies (Tremont-Lukats 2005; Challapalli 2005). In 1998, Kaslo concluded qualitatively (rather than quantitatively) that lidocaine and its oral analogs were effective for relieving pain due to nerve damage, but not necessarily

for pain related to cancer (Kaslo 1998). Later, Tremont-Lukats concluded that lidocaine and its oral analog, mexiletine, were superior to placebo, and as effective as other analgesics for reducing neuropathic pain (Tremont-Lukats 2005). Shortly thereafter, Challapalli published a Cochrane version of the review by Tremont-Lukats, with similar conclusions (Challapalli 2005).

Until now, most trials of IV lidocaine that have been included in existing systematic reviews assessed end-points only immediately post-treatment. Therefore, an important objective of the current review was to search for recent studies (after 2005) in the hopes of uncovering efficacy data over longer follow-up periods. However in contrast to earlier reviews, which examined the efficacy of both IV lidocaine and oral analogs together, the current review examined the efficacy of IV lidocaine only. Also, whereas previous reviews automatically excluded unblinded studies, the current review intended to include unblinded studies as long as control treatment consisted of an active intervention that was likely to duplicate any conceivable non-specific effects of an injected intervention.

## Objectives

### Primary

- To determine if IV lidocaine relieves chronic pain
- To quantify the degree of pain relief, if any, associated with IV lidocaine in comparison to IV placebo and other analgesics

### Secondary

- To assess the safety of IV lidocaine in comparison to placebo and other control analgesic drugs.

## Methods

### Criteria for considering studies for this review

#### *Types of studies*

The current review focused on RCTs with parallel or cross-over designs comparing IV lidocaine to placebo or any active, or putatively active, drug. Dose-response studies of

lidocaine were also analyzed. Blinded as well as unblinded trials were included, however to minimize biases due to differential patient expectations and other nonspecific effects, unblinded studies were included only if they employed a comparably administered (i.e. injected) active control intervention.

Studies had to be published in full journal format or be available as an electronically indexed summary clinical trial report. Unpublished studies were not actively pursued unless specifically referred to within other retrieved articles.

### ***Types of participants***

Patients of any age with chronic pain, defined as pain present for longer than three months' duration, were included. Chronic pain patients included but were not limited to those with the following underlying musculoskeletal and/or neuropathic conditions:

- Neck pain or back pain
- Spinal cord injury
- Post-herpetic neuralgia
- Complex regional pain syndrome type I (reflex sympathetic dystrophy) and type II (causalgia)
- Post-amputation pain
- Fibromyalgia

Chronic pain patients with unrelated cancer were not intentionally excluded, however patients with either neuropathic or non-neuropathic pain directly attributable to cancer (e.g. pain due to compression plexopathy, or pain due to local presence of bony metastases) were excluded.

### ***Types of interventions***

The experimental intervention of interest was systemic lidocaine, administered by IV route. Studies of oral analogs and topical lidocaine were excluded.

Permitted control interventions included active and inactive placebos, and any known, or only putatively, active medical interventions for pain management such as other IV analgesics, regional blockade, anticonvulsants, and antidepressants.

### **Types of outcome measures**

The following hierarchy of outcome measures and endpoints was used:

1. Post-treatment intensity of spontaneous (as opposed to evoked) pain, as assessed by visual analogue scale (VAS) or other validated pain measurement scale
2. Relative reduction in baseline VAS pain intensity by 50% or more
3. Relative reduction in baseline VAS pain intensity by 30% or more
4. Counts of adverse effects, defined as any untoward symptom due to lidocaine with enough intensity to result in study withdrawal or dropout (severe), a reduction in the administered dose (moderate), or no reduction in administered dose (mild).

For this review, outcomes during a period of 1 to 2.9 months post-treatment were of main interest. We speculated, *a priori*, that any benefit of infused lidocaine should persist for *at least* 1 month in order for it to be considered a feasible and effective supportive intervention for work-disabled patients with chronic pain. To make optimum use of the data, however, we planned to extract follow-up data at all available time points and summarize these measurements within multiple time categories. However, due to a paucity of studies employing assessments beyond 24 hours, outcomes were extracted only for the following time periods: '0 to 23 hours' (< 1 day), '1 to 6 days' (< 1 week), '1 to 4 weeks' (< 1 month), and '12 months or longer' ( $\geq$  1 year).

### **Search methods for identification of studies**

The following search terms were used to identify randomized trials and meta-analyses of trials of lidocaine for chronic pain without any initial restrictions on route of administration:

- #1. Randomized clinical trial
- #2. Controlled clinical trial
- #3. Random allocation
- #4. Double blind method
- #5. Single blind method
- #6. Clin\* trial\*

- #7. Placebo
- #8. Random\*
- #9. Research design
- #10. Comparative study
- #11. Prospective stud\*
- #12. Cross-over
- #13. Crossover
- #14. Factorial
- #15. Systematic review
- #16. Metaanalysis
- #17. Meta-analysis
- #18. Metaan\*
- #19. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10  
or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
- #20. Lidocaine
- #21. Lignocaine
- #22. #20 or #21
- #23. #19 and #22
- #24. Chronic pain
- #25. Neuro\* pain
- #26. #24 or #25
- #27. #23 and #26
- #28. Remove duplicates

## ***Electronic searches***

The search strategy was based on methods used by other reviewers (Challapalli 2005), whose approach was in turn described elsewhere (Lefebvre 2001), and then adapted to the following electronic databases:

1. EBM Reviews (2<sup>nd</sup> Quarter 2009):
  - a. Cochrane Central Register of Controlled Trials (CENTRAL);
  - b. Cochrane Database of Systematic Reviews (CDSR);
  - c. Database of Abstracts of Reviews of Effects (DARE);
2. EBM Reviews (3<sup>rd</sup> Quarter 2009):
  - a. Cochrane Methodology Register (CMR);
  - b. Health Technology Assessment (HTA);
  - c. NHS Economic Evaluation Database (NHSEED);
3. ACP Journal Club (January 1991 to June 2009);
4. BIOSIS Previews (January 1969 to December 2008);
5. EMBASE (January 1980 to 2009 Week 27); and
6. MEDLINE (January 1950 to July 2, 2009)

## **Data collection and analysis**

### ***Selection of studies***

All titles and abstracts identified in the search were screened for relevance. Studies that clearly violated eligibility criteria during initial screening were excluded while remaining articles were acquired and reviewed in full text. All full text articles were read by only one review author (JAQ). Non-English papers were not translated, but were scanned for references to other potentially relevant studies.

### ***Data extraction and management***

When possible, information was collected regarding patient characteristics (age, gender, main diagnosis, inclusion/exclusion criteria, number of participants, number of participants randomized, number of and reasons for withdrawals or drop-outs), location and setting, study methods (sequence generation, allocation concealment, degree of blinding, intention-to-treat or results of published analysis), interventions, and outcome measurements (of pain and adverse effects).

Although a second independent reviewer was not used, data were extracted from full text articles and entered directly into a Microsoft Access 2003 database on two separate occasions. Afterward, two separate databases (one for each set of extractions) were validated against each other. Disagreements on any items between databases were resolved by a third reading of the relevant article.

### ***Assessment of risk of bias in included studies***

In keeping with current Cochrane recommendations, study quality scores were not employed. Instead, the methodological quality of each study was assessed using the Cochrane Collaboration tool for assessing risk of bias according to the following criteria (Higgins 2009):

1. Adequacy of random sequence generation;
2. Adequacy of allocation concealment prior to and at the time of recruitment;
3. Degree of blinding of participants, study personnel, and outcome assessors from allocation after recruitment;
4. Adequacy of treatment of incomplete outcome data;
5. Freedom from selective outcome reporting;
6. Other probable biases.

For each criterion, trials were categorized as exhibiting either a 'low', 'unclear', or 'high' risk of bias.

### ***Measures of treatment effect***

#### **Continuous outcomes**

Mean post-treatment pain intensity, as assessed on a 100 mm visual analogue scale (VAS-101) or 0-to-100-point numerical rating scale (NRS-101), were the primary outcomes of interest. Pain intensity measurements that were reported on either a 0-to-10-centimeter VAS (VAS-11) or 0-to-10-point numerical rating scale (NRS-11) were linearly transformed to scores out of 100.

Mean differences in VAS and NRS-based measures between groups were pooled by calculating the weighted mean difference (WMD). For studies that reported pain

outcomes on different scales, the results were standardized to a uniform scale and pooled using the standardized mean difference (SMD) method (Deeks 2009).

### **Dichotomous outcomes**

For studies reporting the number of patients experiencing dichotomous responses, outcomes were analyzed by calculating an odds ratio (OR) and its 95% confidence interval (CI) for each pair-wise comparison between treatment groups. The dichotomous outcomes of primary interest were:

1. A 30% relative reduction in pre-treatment pain score;
2. A 50% reduction in pre-treatment pain score; and
3. Any adverse effects, particularly those leading to treatment modification, dropout or withdrawal.

### ***Unit of analysis issues***

In meta-analysis, it is not unusual to see pooling of multiple comparisons derived from multiple treatment arms within the same study. However when participants in 'shared' comparison arms from the same study are counted more than once, both the sample size and corresponding weight of results from that study are spuriously increased within the pooled results.

For the current review, this type of 'unit of analysis error' was reduced by dividing up the total sample size equally among any shared comparison groups whenever possible. While this method does not completely correct for correlation between comparisons from shared groups, it does permit approximate investigations for heterogeneity across subgroups without seriously inflating the effective sample size (and corresponding weight) of any individual study within the meta-analysis (Deeks 2009).

For shared comparisons on *continuous* outcomes only the sample sizes for shared comparison groups were adjusted. However for shared comparisons on *dichotomous* outcomes, the numbers of events (i.e. numerators) were also adjusted to reduce spurious inflation of the total number of events within pooled results. When numerators and denominators could not be divided equally between shared comparison groups (due to even numbers of events for odd numbers of comparison groups, or alternatively,

odd numbers of events for even numbers of comparison groups) adjusted numerator and denominator values were rounded off in the direction that favoured a positive result for IV lidocaine. Rounding was performed in this manner to intentionally generate liberal estimates of what were otherwise anticipated to be only modest treatment effects for IV lidocaine.

Also, when analyzing adverse effects, the number of independent patients rather than the number of events (which can occur multiply within an individual patient) was used as the unit of analysis. In studies reporting only the frequencies of multiple adverse events, the number of independent patients experiencing the most frequently reported adverse effect was used as a proxy measure of the overall event experience of each group within pooled analyses. Also, for comparisons in which both groups exhibited a zero cell count, '0' values were replaced by '1' values to permit inclusion of those comparisons within the meta-analysis.

### ***Dealing with missing data***

In cases of missing data due to withdrawals or dropouts, mean pain intensity scores were analyzed as reported. For dichotomous outcomes however, denominators were adjusted whenever possible by including withdrawals in the denominator of the causative treatment group. In this manner, analyses were based (again, when possible) on the numbers of patients randomized rather than just the number of patients completing treatment.

### ***Assessment of heterogeneity***

A formal test of statistical heterogeneity between studies was performed using the Cochran Q (Chi<sup>2</sup>) test. Also, the I<sup>2</sup> statistic was used to quantify the percentage of variability in effect estimates that was due specifically to heterogeneity rather than sampling error or chance (Deeks 2009).

### ***Assessment of reporting biases***

A comparison of search results, and analysis results between the current review (i.e. published studies only) and previous reviews (i.e. both unpublished and published studies) was performed. Also, funnel plots were inspected for evidence of asymmetry in the association between effect size and sample size.

### **Data synthesis**

Descriptive measures (means, change scores, and standard deviations) from raw data were estimated in Microsoft Excel 2003. All other analyses were performed in Review Manager 5.0.23 (Review Manager 2008).

Whenever possible, the mean difference in change scores was used in pooled analyses with negative (or positive) change scores indicating the degree of improvement (or worsening). If change scores and standard deviations of the change scores were not reported, these were calculated whenever possible from the raw data within the original articles. When raw data for these measures were not available the mean and standard deviation of post-treatment pain scores was used.

When continuous outcomes were assessed over multiple time points, they were organized into the following time categories:

- 0 to 23 hours (< 1 day)
- 1 to 6 days (< 1 week)
- 1 to 4 weeks (< 1 month)
- 1 to 2.9 months (< 3 months)
- 3 to 5.9 months (< 6 months)
- 6 to 11.9 months (< 1 year)
- $\geq$  1 year

When outcomes were assessed at multiple time points within a single time category, the mean of all measurements within that category was used.

The  $I^2$  statistic was assessed to judge whether a random- or fixed-effects model was used for meta-analysis. If  $I^2$  was less than 50%, a fixed-effects meta-analysis was performed. If  $I^2$  was 50% or greater, a random-effects meta-analysis was used.

For some studies that failed to either sufficiently report summary data or show raw data needed to calculate summary data for meta-analysis (Baranowski 1999; Marchettini 1992; Wallace 2000) approximate measures were imputed from the graphs of point estimates and error bars. For imputation, graphical images were captured from electronic articles and digitized using Engauge Digitizer software (Mitchell 2002). This

method of imputation was validated by comparing the imputed data for two studies (Marchettini 1992; Baranowski 1999) to the reported numerical data for these same articles in an earlier systematic review (Challapalli 2005).

For studies in which pain outcome data were presented non-parametrically as medians, ranges and percentiles, the standard deviations were estimated using tables of conversion factors (White 1979) based on Snedecor's method of determining range/standard deviation ratios for different sample sizes (Snedecor 1946).

In this review, IV lidocaine was designated the 'experimental' treatment while all others were designated as comparators regardless of how they were referred to in the original articles.

### ***Subgroup analysis and investigation of heterogeneity***

Primary subgroup analyses were performed by timing of outcome assessment, and study design (parallel versus cross-over). Secondary subgroup analyses were performed according to underlying condition (central versus peripheral neuropathic pain), and type of control intervention (i.e. placebo versus active controls/analgesics, as well as specific type of analgesic).

### ***Sensitivity analysis***

Sensitivity analyses were conducted to compare model effects (fixed versus random), and pooled estimates with and without outlying studies identified from funnel plots.

## **Results**

### **Description of studies**

#### ***Results of the search***

The search strategy generated 1310 citations, 287 of which were duplicates, leaving 1023 unique citations. After initial screening of unique titles and abstracts, full-text articles of relevant citations, including two earlier systematic reviews of IV lidocaine (Tremont-Lukats 2005; Challapalli 2005) were obtained.

#### ***Included studies***

During full text screening, 35 articles were identified that specifically described a randomized controlled trial involving IV lidocaine as either a control or experimental intervention. On further reading, 20 articles were retained for the current review (Attal

2000; Attal 2004; Barnowsky 1999; Catala 1994; Finnerup 2005; Galer 1996; Gormsen 2009; Gottrup 2006; Kastrup 1987; Kvarnstrom 2003; Kvarnstrom 2004; Lemming 2005; Marchettini 1992; Medrik-Goldberg 1999; Rowbotham 1991; Sorenson 1995; Tremont-Lukats 2006; Wallace 1996; Wallace 2000; Wu 2002).

The majority of trials used a cross-over design with only two studies employing a parallel design (Catala 1994; Tremont-Lukats 2006). Sample sizes ranged from 10 to 33. Both the mean and median sample sizes of the studies were 20.

Six studies were conducted in the United States (Galer 1996; Rowbotham 1991; Tremont-Lukats 2006; Wallace 1996; Wallace 2000; Wu 2002); one was conducted in Israel (Medrik-Goldberg 1999); and ten were conducted in Western Europe. Of the Western European trials, four were conducted in Denmark (Finnerup 2005; Gormsen 2009; Gottrup 2006; Kastrup 1987); two in France (Attal 2000; Attal 2004); one in Italy (Marchettini 1992); one in Spain (Catala 1994); and four in Sweden (Kvarnstrom 2003; Kvarnstrom 2004; Lemming 2005; Sorenson 1995). All studies were single as opposed to multicentre trials.

Within studies, the main underlying conditions included pain after stroke or spinal cord injury (Attal 2000; Finnerup 2005), post-herpetic neuralgia (Barnowsky 1999; Catala 1994; Kvarnstrom 2004; Rowbotham 1991), peripheral neuropathy from a variety of causes including metabolic, traumatic, surgical, compression or idiopathic events (Galer 1996; Gormsen 2009; Gottrup 2006; Kvarnstrom 2003; Marchettini 1992; Tremont-Lukats 2006; Wallace 1996), peripheral neuropathy due specifically to diabetes (Kastrup 1987), lumbar radiculopathy (Medrik-Goldberg 1999), whiplash associated disorder (Lemming 2005), fibromyalgia (Sorenson 1995), complex regional pain syndrome types I and II (Wallace 2000), and chronic extremity pain specifically following amputation (Wu 2002).

The reported mean duration of pain ranged from 9 to 108 months in individual studies, and the weighted mean duration of symptoms across studies was 38 months. Similarly, the reported mean age of patients ranged from 34 to 77 in individual studies, with a weighted mean age of 51 years across studies.

Mean baseline pain intensity for individual studies ranged from 29.1 mm in one study (Barnowsky 1999) to 83.0 mm in another study (Catala 1994). The weighted mean baseline pain intensity across all studies was 55.3 mm.

IV lidocaine was administered at a maximum dose of 6 mg/kg in one study (Catala 1994) with the majority of studies (14) using a dose of 5 mg/kg body weight (Attal 2000; Attal 2004; Barnowsky 1999; Finnerup 2005; Galer 1996; Gormsen 2009; Gottrup 2006; Kastrup 1987; Lemming 2005; Medrik-Goldberg 1999; Rowbotham 1991; Sorenson 1995; Tremont-Lukats 2006; Wu 2002). Other administered doses were 4 mg/kg (Kvarnstrom 2004), 2.5 mg/kg (Kvarnstrom 2003) and 1.5 mg/kg (Marchettini 1992). Furthermore, three studies randomly allocated patients to receive IV lidocaine at more than one dose. Doses of 1 and 5 mg/kg were administered to separate groups in one study (Barnowsky 1999); 2 and 5 mg/kg were administered in another study (Galer 1996); and 1, 3 and 5 mg/kg were administered in another study (Tremont-Lukats 2006).

In terms of inactive controls, IV lidocaine was compared to saline placebo in 14 studies (Attal 2000; Attal 2004; Barnowsky 1999; Finnerup 2005; Gormsen 2009; Gottrup 2006; Kastrup 1987; Kvarnstrom 2003; Kvarnstrom 2004; Lemming 2005; Marchettini 1992; Medrik-Goldberg 1999; Sorenson 1995; Tremont-Lukats 2006), and diphenhydramine with saline placebo in three studies (Wallace 1996; Wallace 2000; Wu 2002). The trial by Galer (1996) also included an unblinded oral mexiletine treatment arm, however only data from the IV treatment arms were considered in this review.

Among trials employing active comparators, IV lidocaine was compared to IV ketamine in four studies (Gottrup 2006; Kvarnstrom 2003; Kvarnstrom 2004; Lemming 2005), IV morphine in three studies (Lemming 2005; Rowbotham 1991; Wu 2002), sympathetic blocks (bupivacaine) in one study (Catala 1994), 'NS1209' (an alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] antagonist) in one study (Gormsen 2009), and IV amantadine in one other study (Medrik-Goldberg 1999).

Eleven studies explicitly mentioned that co-interventions were permitted during the study period. Permitted co-interventions included a range of medications such as simple analgesics (acetaminophen), nonsteroidal anti-inflammatories (acetylsalicylic

acid), simple opioids (codeine), tricyclics, anticonvulsants and anti-epileptics (pregabalin, gabapentin), and spasmolytics (baclofen and tizanidine). Only two studies explicitly stated that co-interventions were *not* permitted on the day of treatment (Kastrup 1987; Lemming 2005). Seven studies did not state one way or the other if co-interventions were permitted during the study.

The follow-up period for most studies was less than 24 hours. Only three studies measured outcomes beyond a 24 hour period: one for five days (Lemming 2005), one for five weeks (Kastrup 1987), and only one for a full year (Catala 1994). Although one additional study assessed outcomes over three weeks, only VAS outcomes on the same day of treatment were reported in any detail (Attal 2000).

### ***Excluded studies***

During full text screening, 15 articles were excluded: one study reported using a 'double-blind controlled' design however it was not clear that random allocation had actually been used (Bach 1990); three studies were published as abstracts and lacked sufficient information to permit an assessment of bias or extraction of data for meta-analysis (Backonja 2000; Glynn 1993; Kastrup 1986); three studies included patients with pain directly attributable to advanced cancer (Bruera 1992; Ellemann 1989; Sjogren 1989); two studies were non-English publications (Ginies 2005; Longas 2005); two studies used the same dose of IV lidocaine within multiple comparison arms, which therefore precluded an assessment of any specific effect of lidocaine (Hord 1992); one study reported a point estimate in the absence of a measure of dispersion or raw data permitting an estimate of standard deviation (Marbach 1988; Viola 2006); one study was of acute pain patients only (Ramamurthy 1995); and one study administered lidocaine using an epidural rather than intravenous route (Glynn 1995).

### **Risk of bias in included studies**

A methodological quality graph and methodological summary figure for included studies are presented in Figures 1 and 2, respectively.

### ***Allocation***

Of the 20 studies included in this review, only five (Attal 2004; Finnerup 2005; Galer 1996; Gormsen 2009; Tremont-Lukats 2006) described a specific method by which their

allocation sequence was generated. Those studies typically indicated that a computer-generated randomization sequence had been used. All other studies claimed to use randomization without otherwise describing how randomization had been performed.

### **Blinding**

Just over half of the studies described explicit methods for maintaining double-blinding. Such strategies included, but were not limited to, the use of:

1. Unaware procedurists (Attal 2000; Attal2004; Gormsen 2009; Marchettini 1999; Sorenson 1995; Wu 2002);
2. Identically administered experimental and control infusions (Attal 2004; Barnowsky 1999; Finnerup 2005; Gottrup 2006; Kvarnstrom 2003; Kvarnstrom 2004; Medrik-Goldberg 1999; Rowbotham 1991; Wu 2002);
3. Preparation of infusions by either a central pharmacy or independent procedurist (Galer 1996; Gottrup 2006; Lemming 2005); and
4. Diphenhydramine in placebo saline to mimic lidocaine side-effects (Wallace 1996; Wallace 2000; Wu 2002).

### **Incomplete outcome data**

Most studies adequately accounted for all recruited patients throughout the entire study period. For some studies (Catala 1994; Sorenson 1995) it was unclear whether the results were based on complete follow-up of all initially recruited patients. In other studies, drop-outs and withdrawals were either unaccounted for or simply excluded (Galer 1996; Gormsen 2009; Kastrup 1987; Wu 2002). Overall, however, losses to follow-up were small, and therefore complete follow-up was usually achieved for more than 80% of patients. One study had a particularly higher drop-out rate (25%) that was apparent only within an earlier published abstract version of the full-text article (Kastrup 1987).

### **Selective reporting**

In 18 studies, outcomes that were originally described in the *Methods* were sufficiently reported in the *Results* of the manuscript. One exception was the study by Lemming (2005) which neglected to report the frequency of side effects within groups after initially presenting this as an outcome. Also, as mentioned earlier, one study followed-up

patients for three weeks but reported outcomes that were measured mainly on the same day of treatment (Attal 2000). Another study supposedly followed-up patients for five weeks but only reported results from immediate-term assessments, or reported raw data for assessments that were performed up to 18 days post-treatment.(Kastrup 1987)

### ***Other potential sources of bias***

Very few studies in this review assessed outcomes beyond one day after treatment. This was either an advertent or inadvertent constraint of the predominant study design that was used (i.e. cross-over design). Consequently, to the extent that positive outcomes for chronic pain are often short-lived, these studies may have been biased towards showing a benefit in favour of IV lidocaine, especially in head-to-head comparisons against placebo. Of the 18 randomized cross-over trials reviewed, 16 assessed outcomes on or within 24 hours of the day of treatment; one assessed outcomes at five days (< 1 week); and only one employed a longer wash-out period and managed to extend follow-up to five weeks, yet reported raw data and summary measures only up to 18 days post-treatment (Kastrup 1987).

Of the two studies employing a parallel design (and which were methodologically suited for long-term follow-up), only one study assessed outcomes at one year (Catala 1994) while the other study terminated at only six hours post-infusion (Tremont-Lukats 2006).

Furthermore, despite the widespread use of a cross-over design, no studies conducted formal assessments to rule-out carry-over and/or sequence effects. In one study (Wu 2002) the possibility of carry-over effects was acknowledged, but not assessed.

Baseline pain and sedation scores were allegedly similar between groups, yet baseline pain scores were not explicitly reported. Finally, in a separate study (Galer 1996) a lidocaine dose of 5 mg/kg was reportedly superior to a dose of 2 mg/kg, however the investigators neither discussed nor adjusted for a 5 mm difference in baseline VAS scores between groups.

## **Effects of interventions**

### ***Comparison 1: IV lidocaine versus placebo or inactive control***

#### **Outcome 1.1: Mean post-treatment VAS or post-treatment change in VAS**

Continuous data on pain relief was extracted from 13 studies (Attal 2000; Attal 2004; Barnowsky 1999; Finnerup 2005; Gormsen 2009; Gottrup 2006; Kastrup 1987; Lemming 2005; Marchettini 1992; Medrik-Goldberg 1999; Rowbotham 1991; Sorenson 1995; Wu 2002). Two studies administered IV lidocaine in two different doses and therefore four shared comparisons were contributed by these two studies. Overall, 15 comparisons were used to estimate the potential benefit of IV lidocaine over IV placebo on continuous measures of pain relief.

Absolute post-treatment pain scores were extracted for 10 studies, while post-treatment changes in baseline scores were extracted for three studies (Attal 2000; Wu 2002; Kastrup 1987). A combined total of 517 patients were treated, 291 of whom were allocated to IV lidocaine and 254 to placebo. Some studies measured outcomes at multiple time points *within* discrete follow-up periods. In those instances, the mean of the measurements within time periods was used in meta-analyses. For two studies (Baranowsky 1999; Sorenson 1995), pain data were not reported numerically and were therefore imputed from digitized graphs.

Furthermore, one study reported results according to two different conditions (post-amputation stump pain and post-amputation phantom pain) rather than according to independent patients (Wu 2002). Among a total of 32 patients, only 11 were experiencing both pain types during the study; nine were assessed for phantom pain only, and 11 were assessed for stump pain only. To include all patients in the pooled analyses, comparisons for the two separate conditions were included. However, to minimize double-counting—and therefore over-weighting—of the results from patients who contributed data for both conditions, approximately one-half of shared patients (6/11) were included in the weight for the phantom pain only group, while the remaining shared patients (5/11) were included in the weight for the stump pain only group in the pooled analyses.

As with studies overall, most in this group did not report outcomes beyond the first day of treatment. One study extended follow-up to five days (Lemming 2005), while another followed-up patients for five weeks, yet only reported detailed VAS data up until 18 days post-treatment (Kastrup 1987).

As Figure 3 shows, the pooled estimate of studies in this group favoured IV lidocaine over placebo (random effects WMD: -10.09; 95% CI: -14.87 to -5.31;  $P < 0.0001$ ). Under a random effects model,  $I^2$  was only 34% and therefore heterogeneity was small. In a sensitivity analysis a fixed effects model was implemented and confirmed a similar result (fixed effects WMD: -9.97 mm; 95% CI: -13.80 to -6.14 mm;  $P < 0.0001$ ).

A funnel plot showed reasonable symmetry in the distribution of positive and negative results among studies of varying sample size on this outcome (Figure 4). Studies of small, intermediate, and large effects appeared to be evenly represented on both sides of the pooled estimate. No studies resided outside of the triangular 95% CI region.

#### **Subgroup 1.1.1: Outcome at 0 to 23 hours (< 1 day)**

A total of 16 comparisons from 11 different studies restricted follow-up to the same day of treatment. For these comparisons, a total of 245 patients were allocated to IV lidocaine and 208 patients were allocated to placebo. One pair of shared comparisons from the same study were associated with point estimates mildly favouring placebo (Barnowsky 1999). All remaining comparisons (14) reported point estimates favouring IV lidocaine, five of which were statistically significant even before pooling.

After pooling, the summarized effect of IV lidocaine in this subgroup indicated that lidocaine was significantly superior to placebo (random effects WMD: -9.97 mm; 95% CI: -13.80 to -6.14 mm;  $P < 0.0001$ ). Heterogeneity in this subgroup of studies was small ( $I^2 = 31\%$ ).

#### **Subgroup 1.1.2: Outcome at 1 to 6 days (< 1 week)**

Between the two comparisons in this subgroup, 31 patients were allocated to IV lidocaine and 31 to placebo. The pooled effect of comparisons involving follow-up after 1 day, but prior to 1 week, indicated that IV lidocaine was not significantly different from placebo (mean difference: -2.63 mm; 95% CI: -13.05 to 7.80 mm;  $P = 0.62$ ). No heterogeneity was evident in these studies, neither qualitatively nor statistically ( $I^2 = 0\%$ ).

### **Subgroup 1.1.3: Outcome at 1 to 4 weeks (< 1 month)**

Only one study reported raw data that permitted calculation of VAS change scores at time points exceeding one week (Kastrup 1987). The total follow-up period in that study was five weeks, however raw data were reported only up 18 days. From this one study, the estimated effect of lidocaine during 7-18 days was based on only 15 patients in each treatment arm. No significant benefit of lidocaine over placebo was observed (mean difference: -3.50 mm; 95% CI: -13.45 to 6.45 mm; P = 0.49).

### **Outcome 1.2: Mean VAS area under the curve**

In one study (Tremont-Lukats 2006) lidocaine was administered in three different doses and therefore three shared comparisons from the same study were extracted for meta-analysis (Figure 5). Most outcome measurements were summarized and reported as medians without corresponding measures of dispersion. However, means and standard deviations were reported for area under the VAS-versus-time curve (AUC). Both the scale and specific method for calculating AUC in that study were unclear; and therefore the reported AUC data and standard deviations were converted to effect sizes (SMDs), which have universal meaning and interpretability.

The pooled analysis showed no effect of lidocaine in comparison to placebo (fixed effects SMD: 0.01; 95% CI: -0.84 to 0.86; P = 0.98). The samples size was small with only 24 patients receiving IV lidocaine and only seven patients receiving placebo. No heterogeneity was detected statistically ( $I^2 = 0\%$ ); however, qualitatively the point estimates for the two lowest doses of lidocaine (1 mg/kg and 3 mg/kg body weight) fell to the right of the null value (slightly favouring placebo) whereas the point estimate for the highest dose of IV lidocaine (5 mg/kg) fell to the left (slightly favouring lidocaine).

### **Outcome 1.3: Mean % change in baseline VAS**

Comparisons of the mean percent change in baseline VAS immediately after treatment was extracted from three studies (Medrik-Goldberg 1999; Wallace 1996; Wallace 2000). A total of 57 patients receiving IV lidocaine were compared to 56 patients receiving placebo (Figure 6). The pooled analysis showed no benefit of IV lidocaine over placebo (random effects WMD: 3.10 percent change; 95% CI: -4.06 to 10.27 percent change; P = 0.40). Heterogeneity was moderate ( $I^2 = 72\%$ ), but was attributable entirely to one study of patients with complex regional pain syndrome (Wallace 2000). Upon removal of

that study from the analysis, statistical heterogeneity disappeared ( $I^2 = 0\%$ ) and the pooled estimate of remaining studies showed a statistically significant benefit in favour of IV lidocaine over placebo (fixed effects WMD: -16.29; 95% CI: -32.25 to -0.33;  $P < 0.05$ ).

#### **Outcome 1.4: Rates of clinically significant pain relief**

As Figure 7 shows, a total of 24 comparisons on rates of clinically significant pain relief were extracted from 10 different studies. Clinically significant pain reduction was defined as a 15 mm *absolute* reduction in baseline VAS in only one study (Kastrup 1987), and variably by a 15, 30, 50 or 100% *relative* reduction in other studies. In this analysis, shared comparison groups were adjusted whenever possible to minimize double-counting of events and patients within subgroups. However, for two studies, the number of comparisons often exceeded the number of events being analyzed (Kastrup 1987; Tremont-Lukats 2006), in which instances unadjusted sample (and event) sizes were used. Sensitivity analyses with and without shared comparisons from individual studies yielded similar pooled estimates (data not show).

Meta-analysis of this group of comparisons was based on 341 participants allocated to IV lidocaine and 329 allocated to placebo (including both shared and unshared participants between and within subgroups). The summary effect estimate for all of these studies combined showed a significant benefit in favour of IV lidocaine over placebo (fixed effects OR: 3.28; 95% CI: 2.20 to 4.88;  $P < 0.0001$ ). The effect of lidocaine was generally consistent across subgroups regardless of whether significant pain relief was defined as a 15 mm absolute reduction (subgroup 1.4.1), or a 15, 30, 50 or 100% relative reduction (subgroups 1.4.2 to 1.4.5, respectively) in baseline VAS score after treatment. Correspondingly, there was no statistical heterogeneity between studies in this group ( $I^2 = 0\%$ ); however, qualitatively the point estimates for comparisons at later follow-up times showed a declining effect of IV lidocaine over time.

#### ***Clinically significant pain relief at 0 to 23 hours (< 1 day)***

First, comparisons that assessed dichotomous outcomes within 24 hours post-infusion were isolated by excluding later assessments from two studies (Kastrup 1987; Lemming 2005). Upon pooling the effects from pair-wise comparisons on outcomes prior to 24

hours of follow-up, IV lidocaine was associated with a greater odds of clinically significant improvement over placebo (fixed effects OR: 3.31; 95% CI: 1.94 to 5.66;  $P < 0.0001$ ). The analysis included three shared comparisons from one study in which lidocaine was administered at doses of 1, 3, and 5 mg/kg body weight (Tremont-Lukats 2006). When this analysis was further restricted to comparisons involving lidocaine at a minimum dose of 5 mg/kg body weight, the pooled effect measure increased only slightly (fixed effects OR: 4.09; 95% CI: 2.29 to 7.29;  $P < 0.0001$ ).

#### *Clinically significant pain relief at 1 to 6 days (< 1 week)*

Only two placebo-controlled trials of IV lidocaine reported or provided raw data permitting calculation of dichotomous improvement at 1 to 6 days of follow-up (Kastrup 1987; Lemming 2005). Across different definitions of clinical improvement, six comparisons were extracted from the two studies. The pooled estimate from these studies indicated a significant benefit of IV lidocaine over placebo (fixed effects OR: 4.29; 95% CI: 2.09 to 8.80;  $P < 0.0001$ ). The estimated odds ratio for a 15-point *absolute* reduction (OR: 4.89; 95% CI: 1.20 to 19.94;  $P = 0.03$ ) was twice as high as the estimated odds ratio for a 15% *relative* reduction (OR: 2.25; 95% CI: 0.38 to 13.47;  $P = 0.37$ ) in baseline VAS scores among lidocaine patients within the same study (Kastrup 1987). Given that no other comparisons used *absolute* reduction as the scale of measurement, the odds ratios for percent *relative* reductions are a more reliable estimate of the true effect of IV lidocaine across different definitions of dichotomous pain relief.

#### *Clinically significant pain relief at 1 to 4 weeks (< 1 month)*

One comparison was extracted from the raw data of a study that permitted an estimate of the effect of IV lidocaine on dichotomous improvement at 1 to 4 weeks (Kastrup 1987). As mentioned elsewhere in this review, the follow-up period for this study was reportedly five weeks, yet outcomes were presented mostly for immediate-term assessments only. Using the raw data for VAS pain scores that were measured only up to 18 days post-infusion, we calculated rates of 15, 30, 50 and 100% percent relative changes in VAS pain scores and, upon pooling these results, found no significant benefit of IV lidocaine over placebo during this period of follow-up (fixed effects OR: 1.38; 95% CI: 0.45 to 4.26;  $P = 0.57$ ).

### *Studies with parallel comparison groups*

Only one placebo-controlled trial in this review used a parallel design (Tremont-Lukats 2006). That study was a dosing trial in which 31 patients were randomly allocated to receive either placebo, or lidocaine at 1, 3 or 5 mg/kg body weight. The point estimate for the effect of lidocaine at 5 mg/kg in that study (OR: 2.50; 95% CI: 0.29 to 21.40) was consistent with the pooled estimate for all other remaining studies that reported rates of dichotomized pain relief (fixed effect OR: 4.84; 95% CI: 2.84, 8.24;  $P < 0.0001$ ). As this particular subgroup analysis was based on only one trial, the results of this part of the analysis must be interpreted cautiously. In the meantime, we did not find evidence of heterogeneity among placebo-controlled studies that might have been due to study design (i.e. parallel versus cross-over).

### **Outcome 1.5: Rates of adverse of events**

For the analysis of adverse event rates, 20 comparisons were extracted from 15 different studies (shown in Figure 8). Some of the more commonly reported mild-to-moderate adverse effects of IV lidocaine were somnolence, light-headedness, headache, nausea, dry mouth and perioral numbness. Due to very low event rates among shared comparison groups from four studies (Attal 2000; Medrik-Goldberg 1999; Rowbotham 1991; Tremont-Lukats 2006), adjusted sample sizes were not used in the pooled analysis.

A total of 329 patients, including double-counted participants, were allocated to IV lidocaine while 323 patients were allocated to placebo. The summary effect measure reflected a significantly higher likelihood of adverse events occurring after lidocaine (fixed effects OR: 7.75; 95% CI: 4.85 to 12.39;  $P < 0.0001$ ). Statistical heterogeneity was nonexistent between, as well as within, subgroups ( $I^2 = 0\%$  for mild-to-moderate event group as well as for withdrawal-causing event group). Qualitatively however, lidocaine patients appeared to be more likely than placebo patients to experience mild-to-moderate adverse events (fixed effects OR: 10.57; 95% CI: 6.26 to 17.82), but no more likely than placebo patients to experience events leading to study withdrawal (fixed effects OR: 1.42; 95% CI: 0.27 to 7.39).

## **Comparison 2: IV lidocaine versus active control**

### **Outcome 2.1: Mean post-treatment VAS or post-treatment change in VAS**

As Figure 9 shows, a total of 10 comparisons on continuous post-treatment VAS pain intensity (or changes in pain intensity) data were extracted from eight separate studies (Catala 1994; Galer 1996; Gormsen 2009; Gottrup 2006; Lemming 2005; Medrik-Goldberg 1999; Rowbotham 1991; Wu 2002). There were 171 patients allocated to IV lidocaine and 200 patients allocated to active comparators. The active comparator in four of these studies was either ketamine (Gottrup 2006), morphine (Rowbotham 1991; Wu 2002) or both (Lemming 2005). However, other studies also compared IV lidocaine to regional sympathetic blocks (Catala 1994), amantadine (Medrik-Goldberg 1999), or NS1209 (AMPA antagonist) (Gormsen 2006). One remaining study in this category compared 5 mg/kg to 2 mg/kg of IV lidocaine (Galer 1996).

A funnel plot of these active-treatment controlled trials showed marked asymmetry in the distribution of positive and negative results by sample size and study precision (Figure 10). The study by Catala resided clearly outside of the triangular 95% confidence region. In comparison to other included studies, this study was clinically and methodologically unique for a number of reasons, including its use of: 1. an unblinded control intervention (sympathetic block with bupivacaine); and 2. longer-term follow-up and assessment of outcomes at one-year post-treatment. Furthermore, the funnel plot for this group of studies provided evidence of possible publication bias by showing a preponderance of smaller (less precise) studies with negative results, and larger (more precise) studies with positive results favouring IV lidocaine.

In any event the pooled estimate showed that, overall, IV lidocaine was no better or worse than other active-treatment controls (random effects WMD: 3.79 mm; 95% CI: -6.87 to 14.46 mm;  $P = 0.49$ ). However, there was considerable heterogeneity among this group of studies ( $I^2 = 79\%$ ). Casewise exclusion of individual trials showed that the majority of heterogeneity was attributable to the one study of regional sympathetic blockade for patients with post-herpetic neuralgia (Catala 1994) The unpooled results of this study indicated that IV lidocaine was significantly worse than regional sympathetic blockade with bupivacaine (mean difference: 28.00 mm; 95% CI: 20.00 to 36.00 mm in favour of bupivacaine;  $P < 0.0001$ ). When excluding this trial from the analysis,

statistical heterogeneity was almost completely eliminated (new  $I^2 = 1\%$ ), yet the pooled effect for the remaining trials still showed that IV lidocaine was no better than active controls (fixed effects WMD: -1.65 mm; 95% CI: -7.16 to 3.87 mm;  $P = 0.56$ ).

### **Subgroup 2.1.1: Parallel study design and later outcome assessment**

As mentioned previously, the study by Catala was also the only active-treatment controlled study to employ a parallel design (Catala 1994). The point estimate from that trial indicated that IV lidocaine was significantly inferior to regional sympathetic blockade (mean difference: 28.00 mm; 95% CI: 20.00 to 36.00 mm;  $P < 0.0001$ ). In contrast, the pooled effect of IV lidocaine from the remaining studies suggested that IV lidocaine was comparable to other active controls (fixed effect WMD: -1.65; 95% CI: -7.16 to 3.87;  $P = 0.56$ ). As this study was also unique with respect to other methodological features (e.g. longer follow-up and use of unblinded controls) study design alone is unlikely to account for the considerable heterogeneity associated with this one study.

### **Outcome 2.2: Miscellaneous summary measures of post-treatment pain relief**

A small number of trials reported other summary measures involving post-treatment pain relief, including the *maximum* percent reduction in pain VAS (Medrik-Goldberg 1999), directly measured pain relief (as opposed to calculated pain relief using pre- and post-treatment pain intensity measurements) (Rowbotham 1991), and ordinal pain intensity ratings on either a four-point scale (Catala 1994), or six-point scale (Galer 1996).

One independent comparison was extracted from each study in this group (Figure 11). A total of 73 patients comprised the IV lidocaine group, while 72 patients comprised the active control group. As each outcome involved a different scale of measurement, SMDs were used to estimate an overall effect size. On miscellaneous measures of pain relief, a small-to-moderate effect size was found in favour of active controls, however the effect was not statistically significant (random effects SMD: 0.43; 95% CI: -0.55 to 1.41;  $P = 0.39$ ). Heterogeneity was observed among this group of comparisons ( $I^2 = 86\%$ ), most of which was again attributable to the trial comparing lidocaine to regional sympathetic block (Catala 1994). Exclusion of this one study resulted in a reduction in heterogeneity (new  $I^2 = 28\%$ ), and weak evidence of a small, non-significant, treatment

effect now favouring IV lidocaine among the remaining three studies (new fixed effect SMD: -0.28; 95% CI: -0.65 to 0.09; P = 0.14).

### **Outcome 2.3: Rates of clinically significant pain relief**

On dichotomous measures of pain relief, seven active-treatment controlled comparisons were extracted from five studies. Clinically significant pain relief was defined as either a 30 or 50 percent post-treatment relative reduction in baseline VAS pain intensity. In unpooled analyses, the point estimates for two shared comparisons involving a study of lidocaine versus NS1209 (AMPA antagonist) fell slightly to the right of the null value and therefore non-significantly favoured lidocaine (Gormsen 2009). In contrast, five comparisons of IV lidocaine versus either IV ketamine or IV morphine showed point estimates slightly to the left of the null value and therefore non-significantly favoured active control treatment. It is noteworthy that no individual comparisons were statistically significant before data pooling. After data pooling, the summary effect measure indicated that, overall, lidocaine was inferior to active-control treatments in a borderline significant manner (fixed effects OR: 0.62; 95% CI: 0.37 to 1.03; P = 0.06).

Across pain relief subgroups, treatment effects were similar regardless of whether improvement was defined as a 30 percent reduction (fixed OR: 0.67; 95% CI: 0.23 to 1.95) or 50 percent reduction (fixed effects OR: 0.60; 95% CI: 0.33 to 1.08) in baseline pain intensity. Correspondingly, statistical heterogeneity was relatively small in this group of studies ( $I^2 = 7\%$ ).

### **Outcome 2.4: Rates of adverse events**

Eight active-controlled trials explicitly reported rates of mild and/or moderate adverse events, and only one study described an incident leading to withdrawal that was attributable to a specific treatment group (Gottrup 2006). The relative odds of adverse events within the active-controlled trials are summarized in Figure 13. In the pooled analysis, 150 IV lidocaine patients were compared to 148 active control-treated patients. The summary effect measure from these trials showed that, overall, IV lidocaine was no worse than other active comparators in producing adverse effects (random effects OR: 0.91; 95% CI: 0.28 to 2.98; P = 0.87). However, moderate heterogeneity was detected among studies reporting incidents of mild to moderate events ( $I^2 = 52\%$ ). Casewise exclusion of individual studies from the analysis indicated that the trial by Medrik-

Goldberg (1999) accounted for more heterogeneity than any other study. Exclusion of that study from the analysis subsequently reduced heterogeneity among the original group of active control-treatment trials by more than half (new  $I^2 = 20\%$ ).

The point estimates of individual studies indicated that, compared to lidocaine-treated patients, the odds of experiencing an adverse event was greater among ketamine and morphine-treated patients, and less among AMPA antagonist- or amantidine-treated patients.

## Discussion

### Summary of main results

#### *IV lidocaine versus placebo*

In comparisons between IV lidocaine and placebo, there was consistent evidence of a benefit in favour of IV lidocaine. Lidocaine appears to be superior to placebo within the first 24 hours after treatment, however for some outcomes the magnitude of the treatment effect is small. The benefit of lidocaine in terms of absolute pain reduction on 100 mm VAS, for example, is approximately 10 mm. For patients with mild pain (i.e. VAS scores  $\leq 30$  mm), an 11 mm difference in VAS score is considered significant, however in patients with *moderate* pain such as those treated within the currently reviewed studies (i.e. VAS scores of 31 to 70 mm), the suggested minimum clinically significant difference (MCSD) is probably closer to 14 mm (Kelly 2001).

Other continuous measures of VAS-based outcomes are not consistently associated with an effect in favour of 5 mg/kg lidocaine over placebo, however comparisons utilizing these other outcomes are currently few in number and samples are correspondingly small. Three shared comparisons from one study were based on mean AUC measurements after separate doses of lidocaine (Tremont-Lukats 2006). None of these doses was associated with a significant benefit over placebo.

Three studies reported mean percent changes in VAS scores (Medrik-Goldberg 1999; Wallace 1996; Wallace 2000). Two of the studies showed a clinically significant, but statistically non-significant, effect in favour of lidocaine infusion (Medrik-Goldberg 1999; Wallace 1996). One remaining study indicated that lidocaine was no different from placebo (Wallace 2000). The only unique feature of the latter study was that it was

performed on patients suffering exclusively from complex regional pain syndromes (CRPS types I and II).

On dichotomous pain relief outcomes, the direction of effect within studies employing IV lidocaine at 5 mg/kg consistently favoured lidocaine in the short-term. Overall, patients treated with IV lidocaine were approximately four times more likely to report clinically significant pain relief on a dichotomous scale than patients receiving only placebo. Data from two studies indicated that the higher odds of experiencing clinically significant pain relief from lidocaine persisted beyond the day of treatment (Kastrup 1987; Lemming 2005), but not during later follow-up at 7-18 days (Kastrup 1987). In the latter study, lidocaine was associated with a four-fold increase in the odds of significant pain relief on the day of treatment, but no significant increase in the odds of pain relief at 7-18 days' follow-up.

Rates of reported mild-to-moderate adverse events (not leading to drop-out or study withdrawal) are consistently greater among lidocaine groups than placebo groups, however rates of serious events (resulting in study withdrawal or dropout) are similar between the lidocaine and placebo patients. Rates of serious events are extremely rare however, and given the small event probabilities and sample sizes involved, existing results about the risk of serious events after IV lidocaine must be interpreted cautiously.

### ***IV lidocaine versus active treatments***

In terms of post-treatment absolute VAS scores and post-treatment VAS change scores, no statistically significant benefit was found in favour of IV lidocaine relative to other active treatments. Overall, lidocaine is therapeutically comparable to other analgesics, at least on the day of treatment. On the other hand, heterogeneity was observed between studies. From a qualitative perspective, the point estimates from individual comparisons indicated directions of effect that moderately favoured 5 mg/kg lidocaine over other active comparators such as NS1209 (Gormsen 2009), amantadine (Medrik-Goldberg 1999) or lower (2 mg/kg) doses of lidocaine (Galer 1996).

On the other hand, individual point estimates from studies comparing IV lidocaine to IV morphine indicated non-significant treatment effects in both directions (Lemming 2005; Rowbotham 1991; Wu 2002), while those comparing IV lidocaine to IV ketamine

generally showed non-significant treatment effects favouring ketamine (Gottrup 2006; Lemming 2005).

One study uniquely showed that lidocaine was very significantly *inferior* to sympathetic blockade for post-herpetic neuralgia (Catala 1994). Pooling of all other comparisons, with and without the latter study, suggest that, overall, IV lidocaine is not significantly better than other active treatments at improving VAS pain scores. If anything, the point estimate after data pooling suggested a direction of effect favouring other analgesic treatments, albeit non-significantly.

The abovementioned results were also mirrored by comparisons based on other summary measures of pain relief, including maximum percent reductions in baseline VAS scores (Medrik-Goldberg 1999), direct (as opposed to calculated) VAS ratings of pain relief (Rowbotham 1991), and post-treatment ordinal pain intensity scores (Catala 1994; Galer 1996). However (and perhaps more significantly), comparisons based on dichotomous measures of clinically significant pain relief generally favoured the active control treatments.

Finally, in pooled analyses, rates of mild to moderate adverse events were comparable between lidocaine and other analgesic groups. The summary effect measure indicated equivalence between lidocaine and active comparators, however both qualitative and statistical heterogeneity were observed among the studies, and this appeared to be attributable to underlying differences in the doses utilized between studies. In this regard, compared to higher-dose lidocaine (5 mg/kg) treatment, the frequency of mild-to-moderate adverse events is greater after higher-dose ketamine (0.4 mg/kg) or morphine treatment; equivalent with lower-dose ketamine (0.1 mg/kg), sympathetic blockade (bupivacaine) or lower-dose lidocaine (2 mg/kg); and lower after NS1209 or amantadine treatment, even if not always significantly so.

### **Overall completeness and applicability of evidence**

Virtually all of the studies included in this review were performed in developed countries. Studies from undeveloped countries and of patients managed outside of a hospital-based pain setting were poorly represented among these studies.

There was no description of study patients by compensation status and therefore the findings of this review are not necessarily generalizable to claimants receiving workers' compensation.

Just over half of the included trials permitted the use of other analgesic co-interventions during the study period. The results of this review are therefore equally applicable to chronic pain patients treated with IV lidocaine alone, and patients treated with IV lidocaine as an adjunct to usual medical therapy.

As emphasized in other sections of this review, the majority of included studies only examined the immediate-term effect of lidocaine. Few studies assessed outcomes at later time points.

Regarding the adverse effects of lidocaine, the majority of studies reported data permitting an estimation of the relative odds of experiencing adverse events, however the extent to which such events may have affected general function as well as condition-specific quality of life was not assessed.

### **Quality of the evidence**

Most studies (15/20) included in this review failed to explicitly describe their randomization procedure; 15 trials were rated as 'unclear' on this criterion by alleging that random allocation had been performed without otherwise providing a description of how the allocation sequence was generated. However five studies (all of which were placebo controlled trials) were rated 'high' on this criterion. Four of these highly rated trials still reported clinically (although not necessarily statistically) significant point estimates in favour of lidocaine over placebo (Attal 2004; Finnerup 2005; Galer 1996; Gormsen 2009). Only one study showed no difference between lidocaine and placebo (Tremont-Lukats 2006). Overall, the numbers of positive and negative studies and the magnitude of pooled estimates of effects, were distributed evenly among studies that were rated 'high' or 'unclear' in their description of a randomization procedure.

Just over half (11/20) of the studies provided evidence of probable concealment of the allocation sequence. For the remaining studies (9/20) it was simply unclear whether code-breaking by investigators was likely or unlikely to have occurred.

Many studies did not describe whether blinded outcome assessment was performed or not, however 18 studies were assessed a 'high' rating on this criterion by at least reporting evidence of *probable* double-blinding (i.e. through masking of both patients and procedurists from treatment allocation). However, given the higher rate of reported side-effects with lidocaine than with placebo, inadvertent unblinding of patients may have occurred among those experiencing lidocaine-related side-effects. This in turn may have biased some outcomes in favour of lidocaine, particularly in the placebo-controlled trials. On the other hand, in one study that utilized an active-placebo control (diphenhydramine) capable of mimicking common side-effects of lidocaine without disrupting sensory changes, lidocaine at a dose of 5mg/kg body weight still exhibited a clinically and statistically significant benefit over the active-placebo (Wu 2002).

Few studies reported an assessment of the success of blinding, however clear lack of blinding was evident in only one study (Catala 1994). The results of that study did not favour experimental lidocaine, but instead, clearly favoured the active comparator. It is worth emphasizing however that bias due to unblinding is more of a concern when study results favour experimental treatment. However in the Catala study, clinically and statistically significant results clearly favoured control treatment (sympathetic blockade), in which case, the *inferiority* of experimental lidocaine was potentially underestimated.

Four studies did not account for all patients originally randomized in the analysis (Galer 1996; Gormsen 2009; Kastrup 1987; Wu 2002) and two studies did not report all outcomes originally described in the *Methods*. (Attal 2000; Galer 1996). Some studies reported drop-outs and withdrawals that occurred after initiation of treatment without attributing these events to a specific treatment arm.

There was a lack of consistency in both the types and the extent of descriptive statistics that were reported by investigators. Often, mean pain scores were presented in the absence of measures of dispersion. In other instances, P-values were reported in the absence of numerically reported point estimates, standard deviations and/or 95% confidence intervals.

## **Potential biases in the review process**

A genuine weakness of the current review is that the data abstraction from full text articles was performed by only one individual. On the other hand, data abstraction for most studies was performed in duplicate during separate iterations that were conducted six months apart from each other.

Also, this review was susceptible to publication bias as no explicit attempt was made to locate unpublished trials. Apart from scanning the reference lists of relevant trials, we did not actively search for unpublished trials. However, upon comparing our set of relevant trials to those listed by earlier systematic reviewers who had actively searched for unpublished studies, we did not encounter any additional relevant studies.

The funnel plot of placebo-controlled trials was symmetrical and therefore did not show evidence of publication bias. However a funnel plot for active-treatment controlled trials was indeed asymmetrical and therefore suggested the likelihood of publication bias with respect to active-treatment-controlled studies. Apart from one outlying trial that was uniquely unblinded and had employed longer-term follow-up (Catala 1994), there was a complete dearth of higher precision negative studies among active-treatment controlled trials (Figure 10).

## **Agreements and disagreements with other studies or reviews**

The results of the current review are consistent with those of earlier reviews published in 2005 by Tremont-Lukats (2005) and Challapalli (2005). Taken together, the estimates of the effects of IV lidocaine from different reviews appear to be robust to slight differences in study selection. In previous reviews, neuropathic pain due directly to cancer was not an exclusion criterion whereas in the current review such studies were excluded. Also, whereas earlier reviews had excluded unblinded trials, the current review included unblinded trials as long as control treatment involved a minimally invasive intervention with conceivably comparable nonspecific effects.

Despite minor differences in selection criteria, our pooled fixed effect estimate of the difference in pain relief on 100 mm VAS between IV lidocaine and placebo was virtually identical to the corresponding estimate published by Challapalli (fixed effects WMD: -11 mm; 95% CI: -17 to -5 mm; P = 0.0003) (Challapalli 2005). Similarly, our random effects

estimate of the difference in pain relief on 100 mm VAS between IV lidocaine and placebo (random effects WMD: -9.97; 95% CI: -13.80 to -6.14;  $P = < 0.0001$ ) was very similar to the corresponding random effects estimate published by Tremont-Lukats (random effects WMD: -10.02; 95% CI: -16.51 to -3.54;  $P = 0.002$ ) (Tremont-Lukats 2005).

Furthermore, in comparisons between IV lidocaine and active control treatments, our pooled estimate of the difference in pain relief on 100 mm VAS (random effects WMD: 3.79 mm; 95% CI: -6.87 to 14.46 mm;  $P = 0.49$ ) varied only slightly from corresponding estimates by earlier reviewers. This small difference was almost entirely attributable to one unblinded study that we included comparing lidocaine to sympathetic regional blockade over a one year period (Catala 1994). Upon removal of that unique study from our analysis the pooled estimate (random effects WMD: -1.62; 95% CI: -7.17 to 3.93) was again almost identical to that of corresponding estimates reported by Challapalli (-0.6 mm; 95% CI: -7 to 6 mm)(Challapalli 2005) and Tremont-Lukats (random effects WMD: -0.6; 95% CI: -6.96 to 5.75) (Tremont-Lukats 2005).

On dichotomous outcome measures of clinically significant pain relief our pooled estimate of the effect of IV lidocaine in placebo-controlled trials was similar to corresponding estimates reported by Challapalli (2005). Also similar to earlier reviews, the current review analyzed studies according to timing of outcome assessment, in which case we found that the odds of pain relief for patients with longer follow-up periods was maintained during, but not after, one week post-treatment. This finding is to be interpreted cautiously however as it based only on shared comparisons from one study that reported outcomes up three days (Lemming 2005), and one additional study that reported outcomes for up to 18 days (Kastrup 1987). More importantly, the latter study had a 25% drop-out rate that was not disclosed in the full text article, but had been reported within an earlier abstract version of the same trial.

Regarding the frequency of adverse events between groups, our pooled estimate of the relative odds of adverse events among IV lidocaine groups versus placebo groups was based on a fixed effects model. To compare our results more directly to those of earlier reviewers, we also estimated a random effects odds ratio (random effects OR: 7.43;

95% CI: 4.49 to 12.29), which ended up being larger than corresponding estimates by Challapalli (random effects OR: 4.60; 95% CI: 3.04 to 6.97) and Tremont-Lukats (random effects OR: 4.16; 95% CI: 2.68 to 6.46) (Challapalli 2005; Tremont-Lukats 2005). The direction of the effect however was the same, and our range estimate (confidence interval) overlapped considerably with the range estimates reported by earlier reviewers. Also, in comparisons of IV lidocaine to other analgesics, our pooled estimate of the relative odds of adverse events (random effects OR: 0.91; 95% CI: 0.28 to 2.98) was again very similar to those reported by Challapalli (random effects OR: 0.78; 95% CI: 0.15 to 3.96) and Tremont-Lukats (random effects OR: 1.21; 95% CI: 0.32 to 6.90) (Challapalli 2005; Tremont-Lukats 2005).

# Authors' conclusions

## Implications for practice

Earlier reviewers have concluded that lidocaine is better than placebo and is as effective as other analgesics. We would emphasize that this conclusion is applicable mostly to the first 24 hours and possibly during the first week, but probably not after the first week after treatment.

We also emphasize that the observed overall treatment effect of a 10- or 11-point difference on a 100 mm VAS in favour of lidocaine over placebo (again, mainly during the first day of treatment) may represent a MCSD for patients with low-intensity baseline pain (VAS  $\leq$  30 mm), but probably not for patients with moderate (31 to 70 mm) or severe ( $>$  70 mm) pain at baseline such as those patients treated in the studies included in the current review (Kelly 2001).

Overall, it can be said that IV lidocaine at a dose of approximately 5 mg/kg body weight has a clear benefit of relieving chronic pain immediately post-infusion, however its efficacy beyond the day of treatment remains unclear. On the one hand, mean improvements in continuous measures of pain relief do not indicate a benefit beyond 24 hours of follow-up. On the other hand, dichotomous measures of pain relief indicate a sustained benefit during, but not after, the first week of follow-up. Again, the results concerning the efficacy of lidocaine specifically after 24 hours must be interpreted cautiously as that evidence is based on a very limited number of studies.

Until the concept of daily-administered IV lidocaine becomes feasible, current evidence does not support the use of IV lidocaine in the routine management of chronic pain. In contrast to oral analogs, which can be feasibly administered daily and therefore exert a prolonged benefit (for as long as daily treatment is maintained), IV lidocaine is invasive (minimally, but invasive nonetheless) and requires specialized equipment, trained personnel, and an actively monitored environment. As repeated IV lidocaine treatments would not be feasible over an extended period, the fate of this intervention will, in the future, depend on its ability (or failure) to show a lasting benefit after either a single infusion or a reasonably limited number of repeat-infusions. In the meantime, current

evidence suggests that single-infusion IV lidocaine offers no benefit beyond one day (or possibly one week) post-treatment.

The current review did not analyze studies of mexiletine, however comparisons between IV lidocaine and mexiletine are relevant to current discussions on the feasibility of IV lidocaine for chronic pain. While Challapalli reported that both lidocaine and mexiletine were efficacious after 24 hours (Challapalli 2005), an estimate of the effect of lidocaine after 24 hours was not presented separately from an estimate of the effect of mexiletine after 24 hours. In that same review (Challapalli 2005), trials assessing outcomes after 24 hours showed generally larger treatment effects for mexiletine than for lidocaine (which is evident in forest plots appearing within the published review). Heterogeneity between studies was not detected statistically, however it is noteworthy that statistical tests of heterogeneity generally have low power and are, therefore, more useful for ruling-in rather than ruling-out genuine heterogeneity. In the meantime, a legitimate clinical rationale remains for suspecting that IV lidocaine (administered as a single infusion within studies) is not as effective as mexiletine (which has the potential to be administered daily) over longer follow-up periods. Consequently then, it is possible that the pooled estimate combining the two interventions in earlier reviews belies a larger treatment effect for oral mexiletine and a correspondingly smaller treatment effect for single-infusions of IV lidocaine.

### **Implications for research**

The most obvious recommendation for future research on IV lidocaine is the need for long-term follow-up. However given the severe impact that longer follow-up has on overall study duration, it is somewhat understandable why authors choosing to use a cross-over design also opted to forego long-term follow-up. In a cross-over study, patients serve as their own controls by participating in every treatment arm in a random but sequential order and by having their outcomes assessed over identical follow-up periods after each treatment period. Compared to a parallel trial, the time required to complete a cross-over trial is much greater, and is in fact multiplied by a factor equal to the number of treatment (and follow-up) periods in the study. Nonetheless, given the need for long-term outcomes, parallel trials with longer follow-up are essential.

On another note regarding cross-over trials, a strict assumption of a cross-over study is that the effects of interventions administered in earlier treatment periods are temporary and do not carry over into subsequent treatment periods. Clearly, the assumption of a short-lived benefit of lidocaine is not only clinically reasonable but also methodologically necessary in a cross-over trial. In fact, a violation of the assumption of a short-lived benefit of lidocaine fatally threatens the internal validity of (or at least requires a re-analysis of raw data from) all cross-over studies we have analyzed for the current review. Yet an assumption of short-term benefit also has profound implications for the interpretation of the results of existing, and future, studies of IV lidocaine. If pain relief from IV lidocaine is truly only temporary, then its potential *effectiveness* (performance in real world clinical settings) is diminished as a result of its invasive nature, potential for side-effects, and requirement for specialized facilities and a monitored setting. Alternatively, if pain relief from a single infusion (or from even just a limited number of repeated infusions) of lidocaine is conceivable, then the longer-term efficacy and effectiveness of this intervention still needs to be established in parallel trials employing longer-term follow-up.

Ultimately, there is a need for RCTs to assess the efficacy of IV lidocaine over clinically relevant time points. Future RCTs would also do well by including outcome measures that more finely quantify and compare the nature and impact of side effects associated with IV lidocaine relative to other more feasible analgesic interventions (Rathmell 2005). In this regard, we echo the sentiments of Rathmell, who states that it is not clear as to what extent the modest (and currently short-term) benefit of IV lidocaine exceeds its potential undesirable effects (including nausea) which are often less well tolerated than pain (Rathmell 2005). Rathmell further reminds us that without knowing the nature, severity, and interference with treatment of those side effects (as opposed to knowing only their frequencies of occurrence) the extent to which the benefits of lidocaine outweigh its risks is difficult to determine (Rathmell 2005).

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## **Contributions of authors**

JAQ conducted the literature search, completed all initial screening of titles and abstracts; and extracted, tabulated and analyzed the data in duplicate iterations. PGF assisted with data entry and duplicate screening of titles and abstracts. JAQ interpreted all analyses, and prepared and edited all drafts of the manuscript.

## **Declarations of interest**

None.

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# Characteristics of studies

## Included studies

*Attal 2000*

<b>Methods</b>	Prospective, randomized, double-blind, placebo-controlled, two-way cross-over trial. Wash-out period: 3 weeks
<b>Participants</b>	N: 16  Setting: pain centre outpatients (France)  Inclusion: post-stroke or spinal cord injury, daily pain for $\geq 6$ months and of at least moderate severity ( $> 30/100$ at baseline); central nervous system injury confirmed on CT or MRI.  Exclusion: non-neuropathic pain, previous treatment with study drugs, contraindications to use of study drugs (e.g. cardiac failure);  Baseline characteristics: 10/16 women; mean age, 55.1 (SD 12) yrs; post-stroke pain due to hemorrhagic (3), ischemic (2) and lacunar (1) stroke; spinal cord injuries due to syringomyelia (5), post-traumatic myelomalacia (3), and cervical spondylosis with myelopathy (2).  Pain duration: all $\geq 6$ months; median, 47 months;  Baseline pain intensity: mean, 55.9 (SD, 20.8)
<b>Interventions</b>	IV lidocaine: 5 mg/kg over a 30 minute period  Comparators: 0.9% saline placebo  Permitted co-interventions: usual medications "kept to a minimum without subsequent modifications to the dose throughout the study."
<b>Outcomes</b>	Continuous outcome: pain intensity on 0- to 100-mm VAS.  Dichotomous endpoints: 1. complete (100%) pain relief; 2. significant ( $\geq 50\%$ ) relief; 3. moderate ( $\geq 30, < 50\%$ ) relief.  Follow-up: immediate-term - every 15 minutes up to 60 minutes, then 90 and 120 minutes, and 6 hours post-injection; short- to medium-term - 3 weeks after second injection.
<b>Notes</b>	Results at 3 weeks' follow-up were summarized, however no data or specific point/range estimates were reported.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Quote: "The study used a randomized, double-blind, placebo-controlled design." Comment: No details provided about how randomization sequence was allocated.
Allocation concealment?	Yes	Quote: "Each infusion was prepared by a study nurse ... who maintained the blinded nature of the study and performed the randomization." Comment: Probably done.
Blinding?	Yes	Treatment was administered, reportedly, "by an anesthesiologist unaware of the treatment". Also, effects of lidocaine on spontaneous pain did not differ between those who did and did not identify their treatment correctly.
Incomplete outcome data addressed?	Yes	1/16 patients in lidocaine had infusion stopped due to somnolence and lightheadedness, but was still included in analysis on an intention-to-treat basis.
Free of selective reporting?	No	Much of the data for outcomes at 60 minutes post-injection was presented but no detailed reporting of outcomes at 3 weeks.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Attal 2004**

<b>Methods</b>	Randomized, double-blind, placebo-controlled, two-way cross-over trial of lidocaine and saline placebo, followed by an open-label trial of mexiletine. Wash-out period: 13 days.
<b>Participants</b>	N: 22  Setting: pain centre outpatients (France)  Inclusion: $\geq$ 6 months daily spontaneous pain of at least moderate severity ( $\geq$ 40 on 100 mm VAS); Exclusion: non-neuropathic pain, severe depression, nephropathy, alcohol/substance abuse; cardiac failure and severe bradycardia (contraindications to lidocaine or mexiletine use); previous treatment with lidocaine, mexiletine, topical anaesthetics or other sodium channel blockers. Also, no patients had complex regional pain syndrome.  Baseline characteristics: mean age, 50.9 (SD, 16.7) yrs; conditions were traumatic nerve injury (14) and post-herpetic neuralgia (8). Pain duration: mean, 42, (SD, 51) months.  Baseline pain intensity: mean, 54 (SD, 15.5)
<b>Interventions</b>	Iv lidocaine: 5 mg/kg over 30 minutes  Comparator: 1. IV saline placebo (0.9% NaCl) in same volume over 30 minutes; 2. oral mexiletine  Permitted co-interventions: use of opioids, tricyclics and gabapentin were "kept to a minimum" without subsequent modifications to the dose throughout the study period.
<b>Outcomes</b>	Continuous outcome (timing): 1. intensity of spontaneous pain on 0- to 100-mm VAS (0, 15, 30, 45, 60, 90 and 120 minutes, then at 6 hrs after start of infusion); 2. average ongoing pain over past 24 hours (once daily until 2 weeks post-treatment).
<b>Notes</b>	Trial was randomized and double-blinded for lidocaine and saline treatments. This was followed by an open-label component of treatment with mexiletine.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Sequence was computer generated.
Allocation concealment?	Yes	A study nurse generated the sequences and kept them sealed in envelopes until the end of the study.
Blinding?	Yes	Both treatments were administered in the same volume over a 30-minute period by an anesthesiologist who was unaware of the treatment being administered.
Incomplete outcome data addressed?	Unclear	No explicit mention of dropout or withdrawal rates
Free of selective reporting?	Yes	All outcomes in Methods reported on.
Free of other bias?	No	Short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Barnowsky 1999**

<b>Methods</b>	Randomized, double-blind, placebo-controlled, three-way cross-over trial.  Wash-out period: 1 wk
<b>Participants</b>	24 patients  Setting: Not described. Principal author was affiliated with university hospital-based pain management centre (United Kingdom)  Inclusion: post-herpetic neuralgia, $\geq 1$ yr's duration, all with ongoing pain and allodynia, with little or no response to conventional treatment (antidepressants, anticonvulsants, local blocks including sympathetic block)  Exclusion: cardiovascular system or ECG abnormalities; previous history of convulsions or reactions to lidocaine; previous or current treatment with lidocaine or its topical analogs.  Baseline characteristics: mean age, 77 yrs; mean pain duration, 3.25 yrs;  Baseline pain intensity: mean, 29.1 (SD, 38.1)
<b>Interventions</b>	IV lidocaine: higher dose of 5 mg/kg over 2 hrs  Timing: Immediate-term only at 15, 30, 45, 60, 75, 90, 105 and 120 min's from start of infusion  Comparators: 1. IV lidocaine at lower dose of 1 mg/kg; 2. saline placebo.  Permitted co-interventions: usual medication for duration of study.
<b>Outcomes</b>	Continuous outcome: intensity of spontaneous pain on 0 to 100 mm VAS
<b>Notes</b>	Article did not report or provide numerical data to permit calculation of standard deviations for pain outcomes. This information was therefore imputed from a digitized figure graph of point estimates and error bars.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	No details provided.
Allocation concealment?	Unclear	No details provided.
Blinding?	Yes	Probably done. All treatments were administered in identical fashion over a 2-hr period.
Incomplete outcome data addressed?	Yes	No drop-outs or withdrawals.
Free of selective reporting?	Yes	All outcomes listed in Methods were reported (some only graphically rather than numerically).
Free of other bias?	No	Very short-term follow-up only. Also, regarding rates of side-effects/adverse events, exclusion of patients with previous reactions to lidocaine would normally create a conservative bias. On the other hand, patients with previous or current treatment with lidocaine were excluded, and therefore this involved a study of treatment naive patients (with no previous exposure to lidocaine). No assessments of potential period, sequence, or carry over effects.

**Catala 1994**

<b>Methods</b>	Prospective, randomized, parallel trial
<b>Participants</b>	<p>N: 30</p> <p>Setting: university hospital-based pain clinic; patients referred from dermatology service (Spain).</p> <p>Inclusion: post-herpetic neuralgia, <math>\geq 3</math> months' duration, unresponsive to oral amitriptyline, and acetaminophen and codeine.</p> <p>Reported characteristics: Mean age (range) of experimental group, 64.2 (60-75); of control group, 62.2 (45 - 75) years.</p> <p>Pain duration: All <math>\geq 3</math> months (max. 2 yrs); lidocaine group - mean, 8.9 (range, 3-24) months. Control group - mean, 9.2 (range, 3-22) months.</p> <p>Baseline pain intensity: mean, 83 (SD, 7)</p>
<b>Interventions</b>	<p>IV lidocaine: initial bolus of 3 mg/kg body weight, subsequent infusion of 3 mg/kg body weight over 2 hours, on 15 consecutive days.</p> <p>Comparator - active treatment: sympathetic block using bupivacaine 0.25%, 10 ml (stellate block for facial neuralgia) or 15 ml (thoracic paravertebral block for intercostal neuralgia); 2 blocks per week, maximum 6 blocks per patient.</p> <p>Permitted co-interventions: simple analgesics (acetaminophen and codeine).</p>
<b>Outcomes</b>	<p>Continuous outcome: post-treatment pain intensity on 0- to 10-cm VAS</p> <p>Follow-up: Short-medium at 3 months; longer-term at 1 year.</p> <p>Other: 5-item Lettinen test measuring pain intensity, pain frequency, and pain-related analgesic use, incapacity, and sleep disturbance (each item on a 4-point scale).</p>
<b>Notes</b>	<p>Result: IV lidocaine inferior to sympathetic blocks for relieving chronic post-herpetic neuralgia-related pain.</p> <p>Scale of VAS not confirmed. However pre-treatment scores of '8.3' and '8.1' supposedly measured severe pain at study entry in the lidocaine and control groups, respectively, and were therefore assumed to represent scores in relation to a 0-10 cm VAS.</p>

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Quote: "The patients were divided at random into two groups of 15 each." Comment: No other details provided about how allocation sequence was generated.
Allocation concealment?	Unclear	No details provided.
Blinding?	No	Probably not done. Treatment protocol and schedule were different in each group. No reported use of placebo or simulated treatments.
Incomplete outcome data addressed?	Unclear	No details provided. No enumeration of drop-outs, withdrawals, or losses to follow-up.
Free of selective reporting?	Yes	All outcome listed in Methods were reported.
Free of other bias?	No	Longer term follow-up was included in this study. However to the extent that differential nonspecific effects should have favoured lidocaine (experimental treatment) this study possibly underestimated the superiority of sympathetic blocks (control treatment).

**Finnerup 2005**

<b>Methods</b>	<p>Prospective, stratified-, block-randomized, "double-blind", placebo-controlled, two-way cross-over trial.</p> <p>Stratification variable: presence or absence of evoked allodynia or hyperalgesia. Block size: 4. Wash-out period: 6 days.</p>
<b>Participants</b>	<p>N: 26 enrolled; 24 completed the trial.</p> <p>Setting: two spinal cord units and a university-based pain clinic (Denmark)</p> <p>Inclusion: age <math>\geq</math> 18 yrs, neuropathic pain due to trauma or disease of spinal cord or cauda equina, median pain intensity <math>\geq</math> 3 on 0- to 10-point NRS during 1-week baseline period.</p> <p>Reported characteristics: median age (range), 53 (28-66); females 7/24.</p> <p>Median pain duration (range): 1. patients with evoked pain response, 4.5 (1-13) yrs; and 2. patients without evoked pain response, 6.5 (2-12) yrs.</p> <p>Baseline pain intensity: mean, 57.1 (SD, 24.5)</p>
<b>Interventions</b>	<p>IV lidocaine: 250 ml infusion, containing 5 mg/kg body weight, over 30 minutes.</p> <p>Comparator - IV placebo: 250 ml infusion of 0.9% NaCl over 30 minutes.</p> <p>Permitted co-interventions: spasmolytics (baclofen and tizanidine), gabapentin, opioids, and simple analgesics (nonsteroidal antiinflammatories, paracetamol, or acetylsalicylic acid) for pain, all "in a constant and unchanged dose" during trial.</p>
<b>Outcomes</b>	<p>Continuous outcome: lowest post-treatment pain intensity on VAS of 0-100 during study.</p> <p>Dichotomous outcome: number of responders showing <math>\geq</math> 33% reduction of pain intensity by end of study.</p> <p>Follow-up: 1. immediate-term only at 25- and 35-minutes after start of infusion.</p>
<b>Notes</b>	<p>Result: Lidocaine significantly reduced pain compared with placebo immediately after infusion. No significant difference between groups in median pain intensity throughout the week after treatment (data not shown in study).</p>

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Quote: "via a computer-generated randomization list..."
Allocation concealment?	Yes	Quote: "One investigator was provided with sealed code envelopes, one for each patient, containing information on the treatment given, and envelopes were returned unopened to the monitor after study termination." Comment: Despite the use of sealed code envelopes, fixed-block randomization permits prediction of later assignments within blocks. However, in cross-over studies, all patients receive all treatments, therefore de-motivating assignment prediction and biased recruitment.
Blinding?	Yes	Quote: "Identical 250-ml infusions of lidocaine or saline were administered intravenously over a 30 minute period... "The primary outcome measure was evaluated by an investigator unaware of symptomatology, group assignment, and possible adverse effects." Comment: Probably successful. Procedures and protocols were identical between periods. Some, but not all, patients correctly identified the period in which they were receiving active treatment due to experiencing either pain relief (9), adverse events (4) or both (8) in association with active treatment. Analgesic efficacy was no greater among patients who did and did not identify the right treatment because of adverse effects.
Incomplete outcome data addressed?	Yes	Immediate-term outcome: 2/24 dropped-out before receiving any treatment, therefore no selective drop-out in any one particular treatment arm.
Free of selective reporting?	Yes	All outcomes listed in Methods were reported.
Free of other bias?	No	Very short-term follow-up. Also, analysis of difference in median pain intensity during week after treatment was available for 19/26 (73%). No intent-to-treat analysis to account for missing data for very short-term outcome. No assessments of potential period, sequence, or carry over effects.

**Galer 1996**

<b>Methods</b>	<p>Prospective, randomized, "double-blind", two-way cross-over trial (followed by open-label "titration trial").</p> <p>Wash-out period: 1 week.</p>
<b>Participants</b>	<p>N: 10 recruited, 9 contributed pain intensity data.</p> <p>Setting: referrals to university-based multidisciplinary pain centre (United States)</p> <p>Inclusion: chronic neuropathic pain, associated with peripheral nerve dysfunction of variable etiology</p> <p>Reported characteristics: 5/9 women; mean age, 51 (range, 33-73) years; painful conditions included diabetic polyneuropathy (5), focal nerve injuries (2), polyneuropathy of unknown etiology (1), and lumbosacral arachnoiditis (1).</p> <p>Pain duration: all <math>\geq</math> 6 months' duration. Mean, 52.1 (SD, 50.3) months</p> <p>Baseline pain intensity: mean, 41 mm</p>
<b>Interventions</b>	<p>IV lidocaine, 5 mg/kg body weight over 45 minutes</p> <p>Comparator - 1. IV lidocaine, 2 mg/kg body weight over 45 minutes; 2. oral mexiletine</p> <p>Permitted co-interventions: none described in original article.</p>
<b>Outcomes</b>	<p>Continuous outcome: post-treatment pain intensity on 0-100 mm VAS.</p> <p>Follow-up: immediate-term at 15 and 30 minutes during infusion, at end of infusion, and 20, 60, and 120 minutes post-infusion.</p> <p>Other: side-effects checklist</p>
<b>Notes</b>	<p>Comments: Measures of dispersion weren't reported.</p> <p>Result: higher dose IV lidocaine resulted in greater reduction in pain intensity than lower dose IV lidocaine (however difference was not significant).</p> <p>Calculations: mean pain duration, 52 (SD, 50.2) months; standard deviations were not reported for various point estimates and therefore had to be imputed for meta-analysis.</p>

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Quote: "Both infusions were administered ... in random order" and "The University of Washington Investigational Drug Service ... performed the randomization". Comment: Probably done given involvement of a specialized research centre for this particular purpose.
Allocation concealment?	Yes	Quote: "The University of Washington Investigational Drug Service prepared each infusion ..." Comment: Probably done as infusions were prepared and sequenced at a central independent location.
Blinding?	Yes	Quote: "The University of Washington Investigational Drug Service prepared each infusion, (and) maintained the blinding". Comment: Probably done, again, due to involvement of a specialized centre for preparing drugs for this type of investigation.
Incomplete outcome data addressed?	No	90% of patients contributed pain data. 1/10 missing; patient dropped-out due to development of new pain at the site of blood draw at a remote location after first infusion and was excluded from analysis. No mention of which treatment this adverse event was associated with.
Free of selective reporting?	No	All outcomes in Methods were reported. Despite being an outcome, no test of significance was reported for the difference in pain relief scores between groups.
Free of other bias?	No	Very short-term follow-up only. No adjustment for 5 mm difference in baseline VAS scores between higher-dose and lower-dose lidocaine groups. Oral mexiletine control intervention did not simulate potential non-specific effects of intravenously administered lidocaine. No assessments of potential period, sequence, or carry over effects.

**Gormsen 2009**

<b>Methods</b>	Prospective, block-randomized, "double-blind", placebo-controlled, three-way, cross-over trial. Block size: 4; wash-out period: 5-11 days.
<b>Participants</b>	<p>N: 17</p> <p>Setting: neuropathic pain clinic (Denmark)</p> <p>Inclusion: age <math>\geq</math> 18; chronic neuropathic pain after peripheral nerve injury accompanied by brush-evoked or mechanical allodynia for more than 3 months; <math>\geq</math> 4 out of 10 pain intensity on NRS-10 during 1 week baseline period.</p> <p>Exclusion: cardiac, circulatory, liver or kidney disease; conduction abnormalities on ECG, or hypersensitivity to study treatments; previous treatment with study interventions within 30 days; treatment with cimetidine, antidepressants, antipsychotics, antiepileptics (except gabapentin and pregabalin), anticoagulants (except aspirin), sodium channel blockers and <math>\beta</math>-blockers (propranolol and tertatolol) within past 14 days.</p> <p>Reported characteristics: 4/15 women; mean age, 54 (range, 21-66); all Caucasian.</p> <p>Pain duration: <math>\geq</math> 3 months; mean, 45.2 (SD, 40.0) months</p> <p>Baseline pain intensity: mean, 40.9 (SD, 19.9)</p>
<b>Interventions</b>	<p>IV lidocaine: 322 ml saline with 'B combine' (vitamin B to mimic yellow colour of comparator, NS1209) administered as 14 ml injection followed by 77 ml/hour over 4 hours; 100 ml lidocaine (5m/kg body weight) during last 30 minutes of a total 4-hour infusion.</p> <p>Comparators (2): 1. NS1209 (AMPA antagonist), 233 ml (1 mg/ml), administered as injection of 14 ml over 60 seconds, followed by infusion of 77 ml/hour, then 100 ml saline (9 mg/ml NaCl) during last 30 minutes of a total 4-hour infusion. 2. Placebo saline with 'B combine', 14 ml injection followed by infusion of 77 ml/hour over 4 hours.</p> <p>Permitted co-interventions: gabapentin, pregabalin, aspirin and/or opioids, so long as doses were stable and unchanged for <math>\geq</math> 1 week prior to study entry, and during the entire study period.</p>
<b>Outcomes</b>	<p>Continuous outcome: post-treatment decrease in pain intensity on 0-100 VAS.</p> <p>Dichotomous outcomes: 1. responders with <math>\geq</math> 33% pain relief; 2. responders with <math>\geq</math> 50% pain relief.</p> <p>Follow-up: Immediate-term at 4 hours (at end of infusion).</p>
<b>Notes</b>	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	A computer-generated randomization sequence was used.
Allocation concealment?	Yes	Randomization sequence was prepared at a central hospital pharmacy where codes were sealed in envelopes and were returned unopened to a monitor after study termination.
Blinding?	Yes	Quote: "The study was a ... double-blind ... study" and "A doctor not involved in the study prepared the bags used for infusion" Comment: All procedures, and even the appearance (colour) of infusions, were standardized across treatments.
Incomplete outcome data addressed?	No	87% of patients contributed pain data. 2 drop-outs immediately after first treatment (1 due to migraine attack, 1 due to pneumonia) and were excluded from analysis. No mention of which treatments were selectively involved.
Free of selective reporting?	Yes	P-values for all comparisons of outcomes that were listed in Methods were reported. (However no reporting of point estimates and measures of dispersion.)
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Gottrup 2006**

<b>Methods</b>	<p>Prospective, stratified-randomized, placebo-controlled, four-way cross-over trial</p> <p>Stratification variable: starting treatment pair (i.e. randomly receiving lidocaine or placebo first, or randomly receiving ketamine or placebo first). Wash-out period: <math>\geq 2</math> days.</p>
<b>Participants</b>	<p>N: 20 recruited</p> <p>Setting: Patients already attending a university hospital-based neuropathic pain clinic (Denmark)</p> <p>Inclusion: verified nerve injury pain and mechanical allodynia (pain to light touch) and pinprick hyperalgesia for more than 3 months.</p> <p>Exclusion: severe psychiatric disease, polyneuropathy, diabetes mellitus, symptoms originating from contralateral side of injury, or abnormal ECG.</p> <p>Reported characteristics: 7/20 women; mean age, 49 (range, 29-73) yrs; pain locations involved upper extremity only (8), lower extremity only (7), and scapular, intercostal or spinal nerves (5); mechanism of injuries were post-traumatic (9) and after surgery (11)</p> <p>Pain duration: Quote, "more than 3 months"; mean, 37 (SD, 70.3) months</p> <p>Baseline pain intensity: mean, 50 (SD, 19)</p>
<b>Interventions</b>	<p>IV lidocaine: infusion of 1.67 mg/kg body weight for 10 minutes, then 3.33 mg/kg for 20 minutes (total 5 mg/kg body weight over 30 minutes).</p> <p>Comparators (2): 1. IV ketamine hydrochloride, bolus infusion of 0.1 mg/kg over 10 minutes, then 0.007 mg/kg/minute over 20 minutes (50 mg/ml); and 2. placebo, infusion of 9 mg/ml NaCl (one time versus lidocaine, one time versus ketamine).</p> <p>Follow-up: immediate-term only at 40 minutes after start of infusion.</p> <p>Permitted co-interventions: prior analgesic treatment if stable for <math>\geq 1</math> week prior to study entry and unchanged throughout entire study period.</p>
<b>Outcomes</b>	<p>Continuous outcome: mean pain post-treatment pain on 0- to 100-mm VAS.</p> <p>Dichotomous outcome: responders with <math>&gt; 33\%</math> pain reduction.</p>
<b>Notes</b>	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	No details provided.
Allocation concealment?	Yes	Quote: "One patient ... was excluded from the study ... because of hallucination and aggressive behavior. When the code was broken, it was revealed that he had received ketamine." Comment: Probably done. Investigators were reportedly naive to treatment assignment until assignment code was broken.
Blinding?	Yes	Quote: "To ensure blinding between the experiment 1 and 2 (1st and 2nd treatment pairs) ... (all infusions were administered in the same manner, standardized manner)". Also, "A doctor not involved in the study prepared the bags used for infusion". Comment: Probably done. Treatments were centrally prepared and administered in a standardized, simulated, fashion during each treatment period.
Incomplete outcome data addressed?	Yes	1/20 missing due to drop-out after first infusion (treatment-type unspecified). Although patient with missing data was excluded from analysis, follow-up rate for pain intensity was 95%.
Free of selective reporting?	Yes	All outcomes listed in Methods were reported.
Free of other bias?	No	Very short-term follow-up. Most patients (14/20) were on analgesics during the study. Presence of co-interventions may have resulted in underestimation of effect of IV lidocaine among non-medicated patients. No assessments of potential period, sequence, or carry over effects.

**Kastrup 1987**

<b>Methods</b>	Randomized, double-blind, cross-over trial. Wash-out period: 5 weeks.
<b>Participants</b>	N: According to earlier abstract publication by same investigators, 20 recruited, 15 completed.  Setting: Not described. Principal author was affiliated with hospital-based clinical physiology and nuclear medicine department (Denmark).  Inclusion: chronic painful diabetic neuropathy with more than one of the following symptoms: pain, dysesthesia, paresthesia, nightly exacerbation, and sleep disturbances;  Exclusion: alcohol abuse, vitamin B12 deficiency, uremia, cardiac or hepatic dysfunction, intermittent claudication or infections.  Reported characteristics: median age (range), 47 (27-63) years; 6/15 females  Pain duration: median, 3 (range. 0.5-20) years  Baseline pain intensity: mean, 46.2 (SD, 25.0) mm
<b>Interventions</b>	IV lidocaine: 5 mg/kg body weight over 30 minutes.  Comparator: Isotonic NaCl, 1 ml/kg body weight over 30 minutes.  Permitted co-interventions: none permitted during study.
<b>Outcomes</b>	Ordinal outcome: symptom score based on summation of 0- to 3-point scale (0 = not present, to 3 = severe) ratings of 5 items (pain, dysesthesia, paresthesia, nightly exacerbation, and sleep disturbances)  Timing: before, after, then at 1 day, and weekly for 5 weeks after each infusion.  Continuous outcome: magnitude of pain on 0- to 100-mm VAS.  Timing: twice daily during entire study period (up to 5 weeks after each infusion).
<b>Notes</b>	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Quote: "... patients received in random order intravenous infusion of lidocaine ... and isotonic sodium chloride ... ". Comment: no details provided about how randomization sequence was generated.
Allocation concealment?	Unclear	Quote: "In a randomized, double-blind, cross-over study..." Comment: No specific discussion on how the allocation sequence was concealed.
Blinding?	Yes	Quote: "Under double-blind conditions ... the patients received in random order intravenous lidocaine ... and isotonic sodium chloride ... ". Comment: Double-blinding probably done, however no other discussion was provided to confirm this.
Incomplete outcome data addressed?	No	An earlier abstract publication by these investigators indicated that originally 20 patients were recruited for this study and that 5 dropped-out due to compliance or personal problems.
Free of selective reporting?	Yes	All outcomes in Methods were reported.
Free of other bias?	Unclear	Follow-up was longer than for most studies on this subject, but still only up to 5 weeks. No assessments of potential period, sequence, or carry over effects.

**Kvarnstrom 2003**

<b>Methods</b>	Prospective, randomized, "double-blind", placebo-controlled, three-way, cross-over trial. Wash-out period: $\geq$ 1 week.
<b>Participants</b>	N: 12 Setting: patient under treatment at university hospital-based pain clinic (Sweden) Inclusion: peripheral nerve or root lesion originating from trauma, surgery, or compression; with spontaneous or evoked pain and either "demonstrable sensory deficit or hyperfunction"; age 20-75 yrs; unresponsive to "conventional treatment". Exclusion: drug abuse, cardiovascular disease or previous treatment with study drugs. Reported/calculated characteristics: 5/7 women; mean age, 47 (SD 6.4, range 34-54) yrs; pain locations were groin (1), and radial (1), peroneal (2), intercostal (1), and saphenous (2) nerves; Pain duration (calculated): Mean 5.8 (SD, 4.4; range, 1-15) yrs Baseline pain intensity: mean, 56.8 (SD, 16.7)
<b>Interventions</b>	IV lidocaine hydrochloride: 2.5 mg/kg body weight. Comparators (2) - administered by IV: 1. ketamine hydrochloride, 0.4 mg/kg body weight; 2. NaCl (saline) as placebo, 9 mg/ml Permitted co-interventions: "regular medication including analgesics during the test period"; reported medications included opiates (1), antiepileptics (2), tricyclic antidepressants (2), and guanethidine block (1).
<b>Outcomes</b>	Dichotomous outcome: Greater than 50% reduction of pain intensity on 0.0- to 10.0-cm VAS Follow-up: immediate-term only at 15, 45, 60, 120 and 150 minutes.
<b>Notes</b>	Result: Analgesic efficacy of IV lidocaine not significantly better than placebo. IV ketamine not significantly superior to IV lidocaine, but significantly superior to placebo.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Quote: "The study had a randomized ... design." Comment: no details provided about how sequence was generated.
Allocation concealment?	Yes	Quote: "The randomization codes were kept in sealed envelopes."
Blinding?	Yes	Quote: "As the design was double-blind and lidocaine was given at two different rates, two bottles of each drug were given." Comment: Probably done. Double-blinding was attempted by standardizing and simulating procedures between periods.
Incomplete outcome data addressed?	Yes	Quote: "There were no drop-outs ... "
Free of selective reporting?	Yes	All outcomes listed in Methods were reported.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Kvarnstrom 2004**

<b>Methods</b>	<p>Prospective, randomized, "double-blind", placebo-controlled, three-way cross-over trial.</p> <p>Wash-out period: <math>\geq</math> 4 days.</p>
<b>Participants</b>	<p>N: 10</p> <p>Setting: Not described. Principal investigator's affiliation was with a university-based department of anaesthesiology and intensive care (Sweden).</p> <p>Inclusion: spontaneous, below-level, central neuropathic pain due to spinal cord injury (SCI); American Spinal Injury Association (ASIA) impairment scale classes A, B and C.</p> <p>Exclusion: chronic pain prior to onset of SCI; drug abuse, cardiovascular disease; previous treatment with study drugs (lidocaine or ketamine).</p> <p>Characteristics: 1 female/10 patients; mean age, 45 (range, 30-60) yrs; 9/10 with incomplete cord lesions (ASIA classes B [6 patients] and C [3 patients]); levels of SCI were cervical (5), thoracic (4), and lumbar (1); all patients suffered from "significant pain" despite previous and/or ongoing interventions including anti-inflammatories, opioids, tricyclics, TENS or acupuncture.</p> <p>Pain duration: mean, 9 (range, 2-35) yrs.</p> <p>Baseline pain intensity: mean, 48.2 (SD, 25.9)</p>
<b>Interventions</b>	<p>IV lidocaine: lidocaine hydrochloride, diluted in saline, 2.5 mg/kg body weight, by infusion pump, at rate of 1.0 mg/kg over 10 minutes, then 1.5 mg/kg over 30 minutes.</p> <p>Comparators: 1. IV ketamine hydrochloride, diluted in saline, 0.4 mg/kg body weight over 40 minutes, administered in 2 bottles to mimic lidocaine administration; 2. IV NaCl (saline), 9 mg/ml, administered in 2 bottles.</p> <p>Permitted co-interventions: other analgesics at their usual dose, unchanged during the entire study period.</p>
<b>Outcomes</b>	<p>Continuous outcome: mean Intensity of spontaneous pain on 0.0- to 10.0-cm VAS.</p> <p>Dichotomous outcome: responders achieving &gt; 50% reduction in baseline pain intensity.</p> <p>Follow-up: Immediate-term only at 0 (baseline), 15, 45, 60, 120 and 150 minutes.</p>
<b>Notes</b>	<p>Measures of dispersion for mean maximal percentage reduction in pain intensity were graphically presented but not explicitly reported. No presentation of raw post-treatment VAS scores to permit self-calculation of SD by reviewers.</p> <p>Patients had "significant pain", refractory to conventional analgesics including tricyclics and opioids.</p>

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Quote: "A nurse not involved in the study randomly selected one blank envelope for each experiment ..." Comment: no details provided as to how randomness of selection was ensured.
Allocation concealment?	Yes	Quote: "Randomization code assignments ... were kept in sealed envelopes ... (and a) nurse not involved in the study randomly selected one blank envelope for each experiment and prepared the infusion according to the written instructions in the envelope." Comment: Probably done. Investigators were not involved in treatment assignment or preparation, only administration of treatments afterward.
Blinding?	Yes	Quote: "All tests were performed ... each time at the same place ... by the same investigators using identical procedures." Comment: Probably done. Identical procedures between treatments and investigators were used to maintain blinding of patients. Infusions were prepared by an independent nurse to maintain blinding of investigators.
Incomplete outcome data addressed?	Yes	No drop-outs or withdrawals in the study.
Free of selective reporting?	Yes	All outcomes listed in Methods were reported, albeit mostly in graphical form and in the absence of standard deviation (or standard error) values.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Lemming 2005**

<b>Methods</b>	<p>Prospective, block-randomized, "double-blind", placebo-controlled, four-way cross-over trial.</p> <p>Block size: 12. Wash-out period: 1 week.</p>
<b>Participants</b>	<p>N: 33</p> <p>Setting: university hospital-based pain and rehabilitation centre (Sweden).</p> <p>Inclusion: Quebec Task Force grade II, chronic whiplash associated disorder (WAD).</p> <p>Reported characteristics: 23/33 women. Mean age (SD), 41 (13) yrs; range, 22-64 yrs.</p> <p>Pain duration: Mean duration (SD), 28 (21) months; range, 5-96 months.</p> <p>Baseline pain intensity: mean, 48 (SD, 18)</p>
<b>Interventions</b>	<p>IV lidocaine. Dose: 5 mg/kg body weight over 30 minutes.</p> <p>Comparators (3) - 2 active IV treatments and 1 IV placebo, each administered over 30 minutes: 1. morphine (0.3 mg/kg), 2. ketamine (0.3 mg/kg), and 3. placebo (isotonic saline).</p> <p>Permitted co-interventions: none on days of treatment and testing.</p>
<b>Outcomes</b>	<p>Continuous outcome: post-treatment pain intensity on 100 mm VAS.</p> <p>Dichotomous outcome: responders showing minimum 50% pain relief on 2 consecutive assessments.</p> <p>Follow-up: 1. immediate-term follow-up every 10 minutes during 30-minute infusion, and at 10, 20, 30, 45, 60, and 120 minutes after infusion was completed; and 2. short-term follow-up for 5 days after each pharmacological challenge.</p>
<b>Notes</b>	<p>Result: Mean reductions in mean neck pain intensity were significantly greater for lidocaine, ketamine and morphine when compared to placebo.</p> <p>Calculated results: Mean reductions in neck pain intensity after IV lidocaine (14 [SD, 18] mm) and IV morphine (18 [SD, 22] mm) were not significantly different (P = 0.26 [two-sided paired t-test]).</p>

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	No details provided.
Allocation concealment?	Yes	As this was a cross-over study, all patients received all 4 treatments regardless of initial allocation. Therefore, investigators' normal incentives for code-breaking and selectively recruiting patients into either treatment arm would not have applied here.
Blinding?	Yes	Quote: "The hospital pharmacy made the randomization and delivered the test substances in identical 50 ml bottles." Comment: Preparation and masking of medications through a central pharmacy generally facilitates blinding of providers and patients.
Incomplete outcome data addressed?	Yes	3 patients were excluded from 'later' parts of the analysis, however all patients were included in the analysis of VAS pain scores.
Free of selective reporting?	No	All pain outcomes in the Methods section were reported on in the Results section, however assessment of side-effects was also mentioned in the Methods section and not reported in the Results section.
Free of other bias?	No	No evaluation of possible carry-over or period effects. Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Marchettini 1992**

<b>Methods</b>	Randomized, double-blind, placebo-controlled, cross-over trial Wash-out period: not reported
<b>Participants</b>	N: 10  Setting: university hospital-based pain clinic (Italy)  Inclusion: patients affected by "pain and sensory disorder, following lesions of the peripheral nervous system, and under treatment at a university hospital-based pain clinic.  Exclusion: no criteria specified.  Baseline characteristics: 7/10 women; mean age, 49 (SD, 16); underlying conditions were post-surgical abdominal pain (1), chest and upper extremity pain [after mastectomy (4) or unknown cause (1)], leg pain [after vein stripping (1), harvesting for coronary bypass surgery (1), or diabetic neuropathy (1)].  Baseline pain intensity: mean, 64.1 (SD, 19.6) mm
<b>Interventions</b>	IV lidocaine: 1.5 mg/kg (20 mg/ml)  Comparator: saline infusion, administered in manner identical to that of lidocaine infusion  Permitted co-interventions: none described.
<b>Outcomes</b>	100 mm VAS  Timing: 5, 15, and 35 min's after injection
<b>Notes</b>	Standard deviations were presented graphically but not numerically. Numerical standard deviations were extracted from digitized graphical images.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Quote: "The study was carried out in a ... randomized fashion." Comment: no details provided about how sequence was generated.
Allocation concealment?	Unclear	No details provided.
Blinding?	Yes	Quote: "Both patients and observers were blind to the injections." Comment: Also, procedures were administered in identical manner for both treatments.
Incomplete outcome data addressed?	Yes	No drop-outs or withdrawals.
Free of selective reporting?	Yes	All outcomes listed in Methods reported.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Medrik-Goldberg 1999**

<b>Methods</b>	Randomized, double-blind, placebo-controlled, three-way cross-over trial. Wash-out period: $\geq 2$ days.
<b>Participants</b>	30 patients (28 completed, 2 contributed partial data)  Setting: referrals to orthopaedic surgeons at a medical centre-based "Pain Relief Unit" (Israel)  Inclusion: patients of ages 18-60 yrs with painful lumbar radiculopathy of 3-36 months' duration, presence of herniated lumbar disc on imaging, concordant clinical symptoms; no history of back surgery  Exclusion: cardiac disease, epilepsy, impaired renal or liver function.  Baseline characteristics: 14/30 women; mean age, 34 (SD, 2) yrs; conditions included herniated disc at single level (24), two levels (4), and three-levels (2); levels of herniation involved L4-5 (15), L5-S1 (14), L3-4 (7) and L2-3 (2); mean sciatica pain intensity, 52 (SD, 5).  Pain duration: mean, 16 (SD, 2) months; range, 3-34 months;  Baseline pain intensity: mean, 63 (SD, 21.9)
<b>Interventions</b>	lidocaine: 5 mg/kg body weight, in 500 ml infusion over a 1 to 2-hr period, then switch to normal saline until 3-hr total infusion period reached.  Timing: immediate term only, at every 30 min's up to 3 hrs  Comparators: 1. amantadine, 2.5 mg/kg; 2. saline placebo  Permitted co-interventions: none described
<b>Outcomes</b>	Pain intensity on 100 mm VAS
<b>Notes</b>	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	No details provided.
Allocation concealment?	Unclear	Quote: "... a double-blind, randomized, cross-over trial." Comment: No explicit mention of how the allocation sequence was concealed up to the time of randomization.
Blinding?	Yes	Probably done. Procedures were standardized across all three treatments. Placebo infusions were also switched at 1 to 2 hrs to simulate administration of the experimental treatment.
Incomplete outcome data addressed?	Yes	Probably not an issue. 2/30 dropped-out prior to third treatment: 1 no amantadine treatment, 1 no placebo treatment. Still, 30 patients with complete lidocaine data, and 29 patients with complete amantadine and placebo data.
Free of selective reporting?	Yes	All outcomes in Methods were reported.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Rowbotham 1991**

<b>Methods</b>	<p>Prospective, randomized, "double-blind", placebo-controlled, three-way cross-over trial.</p> <p>Wash-out period: <math>\geq</math> 48 hours.</p>
<b>Participants</b>	<p>N: 19</p> <p>Setting: No details provided. Principal author was affiliated with university-based department of neurology and anaesthesia (United States).</p> <p>Inclusion: post-herpetic neuralgia (PHN)</p> <p>Exclusion: medical contraindications to IV local anaesthetic and opioids; previous neurolytic nerve block or neurosurgical therapy for PHN.</p> <p>Characteristics: 11/19 women; mean age, 70.5 years; location of PHN involved ophthalmic distribution (5), cervical region (1), thoracic region (11), and lumbar PHN (2).</p> <p>Pain duration: all <math>\geq</math> 3 months after healing of skin rash of herpes zoster; mean duration, 46 (range, 4-144) months;</p> <p>Baseline pain intensity: imputed mean, 50 (imputed SD, 30) mm</p>
<b>Interventions</b>	<p>IV lidocaine: target dose of 5 mg/kg, maximum dose of 450 mg (average dose was 316 [range, 180-450] mg).</p> <p>Comparator: 1. morphine, target dose of 0.3 mg/kg body weight, to maximum dose of 25 mg (average dose was 19.2 [range, 11.0-25.0] mg) ; 2. saline (placebo), infused at same rate (in ml/minute over 60 minutes) as lidocaine and morphine infusions.</p> <p>Permitted co-interventions: none described.</p>
<b>Outcomes</b>	<p>Continuous outcomes: 1. mean post-treatment pain intensity on 100-mm VAS, and 2. mean "pain relief score" on 100-mm VAS; 3. side-effects, assessed by measuring 26 common medication effects on a checklist (out of a maximum score of 78).</p> <p>Follow-up: Immediate-term only at 15, 30, 45 and 60 minutes during infusion, and at 30, 60, and 120 minutes after infusion.</p>
<b>Notes</b>	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Quote: "Subjects were randomly assigned ... " Comment: No other details provided.
Allocation concealment?	Unclear	No details provided.
Blinding?	Yes	Procedures for administration were identical between treatment periods.
Incomplete outcome data addressed?	Yes	All patients completed the study, however 1/19 was withdrawn from lidocaine early after experiencing nausea and lightheadedness. Blood level of lidocaine in this patient did achieve therapeutic level, therefore data was included in analysis.
Free of selective reporting?	Yes	All outcomes listed in Methods
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Sorenson 1995**

<b>Methods</b>	Randomized, double-blind, placebo-controlled, two-way cross-over trial Wash-out period: 1 wk
<b>Participants</b>	12 patients (11 completed)  Setting: hospital-based pain clinic (Sweden)  Inclusion: patients with fibromyalgia  Baseline characteristics: mean age, 41 (range, 21-59) yrs; 12/12 females  Pain duration: median, 3 (range, 3-28) yrs.  Baseline pain intensity: imputed mean, 61 (imputed SD, 24.6)
<b>Interventions</b>	IV lidocaine: 5 mg/kg body weight (10 mg/ml) over 30 min.  Comparator: same volume of isotonic saline over 30 min.  Permitted co-interventions: none described.
<b>Outcomes</b>	Pain intensity on 100 mm VAS before and after injection.  Dichotomous outcome: post-treatment reduction in baseline VAS by > 50% or 15 mm  Timing: immediate term at 10, 20 and 30 min during infusion, and at 15, 30 and 60 min after infusion.
<b>Notes</b>	Pain outcome data were presented graphically as medians, ranges and percentiles. For current analyses, medians were used as approximations of means. Standard deviations were imputed by multiplying the range by a factor of 0.3152

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	No details provided.
Allocation concealment?	Unclear	No details provided
Blinding?	Yes	Quote: "This was a double-blind, placebo-controlled study, the patients and the examining physician ... being unaware of which drug the anesthesiologist injected." Comment: the above quote was extracted from an earlier section of the article referring to a separate study of morphine, however it would appear that standard procedures were adhered to for the lidocaine portion of the study as well.
Incomplete outcome data addressed?	Unclear	1/11 dropped-out and therefore did not complete the study; no description if drop-out occurred before, or was associated with one particular treatment arm. The patient's data was likely excluded.
Free of selective reporting?	Yes	All outcomes listed in Methods were reported. However, some pain outcome data were only presented graphically and not numerically.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Tremont-Lukats 2006**

<b>Methods</b>	Prospective, block-randomized, double-blind, placebo-controlled, four-arm, parallel trial Block size: 4.
<b>Participants</b>	<p>N: 31</p> <p>Setting: outpatients treated at a university-based clinical research centre (United States)</p> <p>Inclusion: documented peripheral neuropathic pain, <math>\geq 1</math> yr's duration, of any etiology.</p> <p>Exclusion: total body, nonspecific or non-neuropathic pain; abnormal hepatic or renal function; cardiovascular disease; known hypersensitivity to lidocaine.</p> <p>Characteristics: 22/32 women; mean age (SD) was 49 (15) yrs, 43 (7) yrs, and 35 (9) yrs in the high-/experimental, medium-/control and low-dose/control lidocaine groups, respectively; mean age (SD) in the placebo group was 32 (6) yrs; conditions included complex regional pain syndrome (CRPS) type 1 (18), CRPS type 2 (5), painful peripheral polyneuropathies (5), radicular pain (3), and brachial plexopathy (1).</p> <p>Pain duration: all patients <math>\geq 1</math> yr; reported mean duration (SD) was 4.8 (3.5), 2.7 (2.2), and 2.7 (1.8) yrs in high-/experimental, medium-/control and low-dose/control groups, respectively, and 2.6 (2.0) yrs in placebo group.</p> <p>Baseline pain intensity (in 5 mg/kg dose group): mean, 57 (SD, 21)</p>
<b>Interventions</b>	<p>IV lidocaine: IV lidocaine at 5 mg/kg/hr until patient experienced either complete pain relief or bothersome side-effects, or at 6 hours maximum infusion-time.</p> <p>Comparators: 1. IV lidocaine at 1 mg/kg/hr; IV lidocaine at 3 mg/kg/hr; and 3. saline placebo.</p> <p>Follow-up: immediate-term only during 6-hour infusion and over additional 4 hours after infusion.</p> <p>Permitted co-interventions: other analgesic drugs except lidocaine or its oral analogs (tocainide, mexiletine, or flecainide).</p>
<b>Outcomes</b>	<p>Continuous outcome: pain intensity on 0- to 100-mm VAS; average absolute change; percent change from baseline; area under the VAS versus time curve (AUC) during last 6 hours of follow-up.</p> <p>Dichotomous endpoint: <math>&gt; 30\%</math> mean reduction in baseline pain intensity during last 6 hours of follow-up.</p>
<b>Notes</b>	No reporting of mean post-treatment VAS scores, change scores and corresponding standard deviations. Therefore, reported mean area under the curve (AUC) and SD was included as continuous outcome in meta-analysis.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Quote: "Computer-generated sequences in blocks of four ... randomly allocated patients into one of four treatment arms ... "
Allocation concealment?	Yes	Quote: "To ensure effectiveness of masking, the pharmacy staff prepared placebo or lidocaine at the dose assigned to each patient and gave the prepared, unlabeled study solutions to the nursing staff for immediate administration."
Blinding?	Yes	Quote: "Both patients and investigators were masked to study assignment until the time of data analysis."
Incomplete outcome data addressed?	Yes	Data was lost (during a computer upgrade) for 1 placebo-group patient. No sensitivity analysis for missing values, however this patient otherwise completed the study, and therefore, the data can be considered missing completely at random (MCAR).
Free of selective reporting?	Yes	All outcomes listed in the Methods were reported. A minor concern is that adverse events were reported instead of the numbers of affected patients in each treatment group.
Free of other bias?	No	Very short-term follow-up only.

**Wallace 1996**

<b>Methods</b>	Randomized, double-blind, placebo-controlled, two-way cross-over trial Wash-out period: 1 wk
<b>Participants</b>	11 patients  Setting: referrals to university hospital-based pain service (United States)  Inclusion: neuropathic pain after a peripheral nerve injury; Exclusion: pending litigation at time of study.  Baseline characteristics: 6/11 women; mean age, 52.4 (SD 19.3, range 28-75) yrs; sites of pain (no.) included mandibular (2), upper extremity (3), lower extremity (3), and trunk (3);  Pain duration: all $\geq$ 5; mean, 48.4 (SD, 44.5) months  Baseline pain intensity: mean, 57.9 (SD, 23,8)
<b>Interventions</b>	IV lidocaine: administered by computer-controlled infusion pump, at targeted, stepped plasma concentration levels of 0.5, 1, 1.5, 2, and 2.5 $\mu\text{g/ml}$ for 10 min each unless patients developed unacceptable side effects (arrhythmias, nausea/vomiting, tinnitus, visual hallucination, muscle twitching).  Permitted co-interventions: none described.
<b>Outcomes</b>	intensity of spontaneous pain on 100 mm VAS  Timing: immediate-term, at 4 min post-injection, and every 5 min until completion of infusion
<b>Notes</b>	Point estimates and standard deviations for % reduction in baseline pain VAS were extracted/imputed from digitized graph of means (in % reduction) and error bars.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	No details provided about how sequence was generated.
Allocation concealment?	Unclear	No details provided.
Blinding?	Unclear	No details provided
Incomplete outcome data addressed?	Yes	No mention of drop-outs, withdrawals or missing VAS data for spontaneous pain. Baseline and final post-infusion pain scores were reported for all 11 patients, suggesting that measurements between these two extremes were also collected.
Free of selective reporting?	Yes	All outcome listed in Methods were reported.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Wallace 2000**

<b>Methods</b>	Randomized, double-blind, placebo-controlled, two-way cross-over trial  Wash-out period: 1 wk
<b>Participants</b>	16 patients  Setting: Not stated. Principal author was affiliated with university hospital-based department of anesthesiology (United States)  Inclusion: complex regional pain syndrome (CRPS) I and II with prominent allodynia  Baseline characteristics: 7/16 women; conditions were CRPS I (9), CRPS II (7); mean age, 44 (SD of 15, range of 23-74) yrs;  Mean pain duration, 43 (SD of 34, range of 7-128) months  Baseline pain intensity (heat induced pain): mean, 44.9 (SD, 3.8) mm
<b>Interventions</b>	IV lidocaine: administered by computer-controlled infusion pump, steady plasma levels for 20 minutes at a time at concentrations of 1 µg/ml, 2 µg/ml, and 3 µg/ml.  Comparator: diphenhydramine (dose not reported), which reportedly produces same side-effects as lidocaine without affecting sensory thresholds.
<b>Outcomes</b>	Continuous outcomes: 1. spontaneous pain intensity on 100 mm VAS; 2. side-effect symptom intensity on 100 mm VAS  Timing: Immediate-term only at 20 minutes following end of each infusion  Permitted co-interventions: none described.
<b>Notes</b>	Means and standard deviations for reported pain outcomes (post-treatment % reduction in baseline VAS, and side-effect symptom intensity) were extracted/imputed from digitized graphs for current analyses.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Quote: "The order of the study sessions was randomized ... ". Comment: no other details provided.
Allocation concealment?	Unclear	No details provided
Blinding?	Yes	Probably done. Diphenhydramine was used as placebo to mimic side-effects of lidocaine without affecting sensory thresholds.
Incomplete outcome data addressed?	Yes	All outcomes listed in Methods reported.
Free of selective reporting?	Yes	Probably done. No reported drop-outs or withdrawals.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

**Wu 2002**

<b>Methods</b>	<p>Block-randomized, double-blind, active-placebo-controlled, three-way cross-over trial.</p> <p>Wash-out period: &lt; 1 day. Block size: 12 (to ensure even distribution of patients between 3 treatment groups during first treatment period).</p>
<b>Participants</b>	<p>32 patients (31 completed)</p> <p>Inclusion: ages 18-85; presence of persistent post-amputation pain for &gt; 6 mo.; Exclusion: history of allergic reaction to study drugs; cardiac conduction defects, or myocardial infarction within 3 mo. of enrolment; severe pulmonary disease; current history of alcohol or substance abuse; presence of seizures, dementia or encephalopathy; chronic hepatic disease or hepatic failure; leukopenia or thrombocytopenia; any terminal illness with a life expectancy of &lt; 6 mo.</p> <p>Baseline characteristics: 12/31 female; mean age, 54 (SD, 13) yrs; type of pain, both stump and phantom pain (11), stump pain only (11), phantom pain only (9).</p> <p>Pain duration: all &gt; 6 months; mean, 81 (SD, 87.4) months</p> <p>Baseline pain intensity (of worst symptoms): imputed mean, 50 (imputed SD, 28) mm</p>
<b>Interventions</b>	<p>IV lidocaine: 1mg/kg bolus followed by 4 mg/kg infusion over 40 min, to a max. dose of 400 mg.</p> <p>Comparators: 1. IV morphine, 0.05 mg/kg bolus followed by 0.2 mg/kg infusion over 40 min to a max. dose of 25 mg; 2. active-placebo of diphenhydramine, 10 mg bolus followed by 40 mg infusion.</p> <p>Permitted co-interventions: acetaminophen, NSAIDS, as needed during study period.</p>
<b>Outcomes</b>	<p>Separate pain intensity ratings on 100 mm VAS for 1. stump pain; 2. phantom pain; 3. stump pain relief; and 4. phantom pain relief.</p> <p>Timing: immediate-term only, beginning 30 min pre-infusion, then every 5 min until 30 min after end of infusion.</p>
<b>Notes</b>	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	No details provided
Allocation concealment?	Yes	Quote: "Drugs were prepared by a pharmacist in a way that allowed for administration of an equal volume for each of the three study medications." Comment: Probably done. Preparation of medications through a central pharmacy usually ensures protection of allocation code.
Blinding?	Yes	Quote: "All study medications were identical in appearance ... (and) the investigator administering the study medication was blinded from the outcome assessment ... and the subject and research coordinators were blind to the exact timing of study medication administration." Comment: Probably done. Medication-type was likely masked from patients and investigators.
Incomplete outcome data addressed?	No	1/32 dropped-out because of spontaneous recovery and absence of pain pre-infusion (both arms affected equally). 2/32 with incomplete data due to technical difficulties with intravenous access; no details provided about which treatment arm(s) affected. 2 with incomplete data did not undergo second infusion due to nausea and vomiting from previous day's infusion; again, no details provided about which treatment arm(s) affected.
Free of selective reporting?	Yes	All outcomes in Methods were reported.
Free of other bias?	No	Very short-term follow-up only. No assessments of potential period, sequence, or carry over effects.

## Excluded studies

### *Bach 1990*

<b>Reason for exclusion</b>	A double-blind controlled design was used, however it is not clear that treatment assignment/sequence was determined through randomization. Also, outcome measures included evoked pain sensibility and thresholds, but not measures of spontaneous pain intensity.
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### *Backonja 2000*

<b>Reason for exclusion</b>	Published abstract only.
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### *Bruera 1992*

<b>Reason for exclusion</b>	Study population included patients with neuropathic pain due to advanced cancer.
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### *Ellemann 1989*

<b>Reason for exclusion</b>	Study population included patients with neuropathic pain due to cancer.
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### *Ginies 2005*

<b>Reason for exclusion</b>	Non-English publication.
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### *Glynn 1993*

<b>Reason for exclusion</b>	Abstract-type publication only. Later more detailed publication by same author presented raw data that permitted inclusion in meta-analysis.
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### *Glynn 1996*

<b>Reason for exclusion</b>	Lidocaine was administered by epidural rather than IV route.
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### *Hord 1992*

<b>Reason for exclusion</b>	Lidocaine was used as control intervention for comparison against lidocaine in combination with IV regional bretylium for reflex sympathetic dystrophy. No ability to test for effect of lidocaine in this study.
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### *Kastrup 1986*

<b>Reason for exclusion</b>	Abstract publication only. In contrast, a later detailed publication by the same investigators was included in the current meta-analysis.
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### *Longas 2005*

<b>Reason for exclusion</b>	Non-English publication.
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**Marbach 1988**

<b>Reason for exclusion</b>	Study of parenteral (intranasal lidocaine as active-control for intranasal cocaine). Neither range estimates nor P-values reported or graphically presented for specific point estimates of interest. Insufficient data to impute standard deviations of outcomes for current meta-analysis.
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**Ramamurthy 1995**

<b>Reason for exclusion</b>	Study population consisted of patients with acute pain (< 3 months' duration) only
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**Rocco 1989**

<b>Reason for exclusion</b>	Same dose of lidocaine administered in all treatment arms. Not a study that permitted comparison of lidocaine to placebo, active control, or lidocaine in a different dose.
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**Sjogren 1989**

<b>Reason for exclusion</b>	Study population involved patients with bone pain due to metastatic cancer
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**Viola 2006**

<b>Reason for exclusion</b>	Insufficient data reported to calculate or impute means, standard deviations, or proportions of responders for outcomes used in current meta-analysis.
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# Tables of analyses

**Table 1:  
IV lidocaine versus placebo or inactive control**

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Mean post-treatment VAS or VAS-change	13	545	Mean Difference (IV, Random, 95% CI)	-10.09 [-14.87, -5.31]
1.1.1 VAS at 0 to 24 hours (< 1 day)	11	453	Mean Difference (IV, Random, 95% CI)	-12.35 [-17.88, -6.82]
1.1.2 VAS at 1 to 6 days (< 1 week)	2	62	Mean Difference (IV, Random, 95% CI)	-2.63 [-13.05, 7.80]
1.1.3 VAS at 1 to 4 weeks (< 1 month)	1	30	Mean Difference (IV, Random, 95% CI)	-3.50 [-13.45, 6.45]
1.2 Mean VAS area under the curve	1	31	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.84, 0.86]
1.2.1 AUC at 0 to 24 hours (< 1 day)	1	31	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.84, 0.86]
1.3 Mean % change in baseline VAS	3	113	Mean Difference (IV, Fixed, 95% CI)	3.10 [-4.06, 10.27]
1.3.2 % VAS change at 0 to 24 hours (< 1 day)	3	113	Mean Difference (IV, Fixed, 95% CI)	3.10 [-4.06, 10.27]
1.4 Rates of clinically significant pain relief	10	690	Odds Ratio (M-H, Fixed, 95% CI)	3.28 [2.20, 4.88]
1.4.1 Absolute pain reduction > 15 mm on VAS	1	40	Odds Ratio (M-H, Fixed, 95% CI)	4.89 [1.20, 19.94]
1.4.2 Percent change > 15%	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.52, 6.80]
1.4.3 Pain reduction > 30%	6	220	Odds Ratio (M-H, Fixed, 95% CI)	2.70 [1.41, 5.18]
1.4.4 Pain reduction > 50%	8	278	Odds Ratio (M-H, Fixed, 95% CI)	4.38 [2.31, 8.32]
1.4.5 Pain reduction = 100%	2	112	Odds Ratio (M-H, Fixed, 95% CI)	2.07 [0.36, 11.74]
1.5 Rates of adverse events	15	652	Odds Ratio (M-H, Fixed, 95% CI)	7.75 [4.85, 12.39]
1.5.1 Mild to moderate events	15	522	Odds Ratio (M-H, Fixed, 95% CI)	9.04 [5.50, 14.86]
1.5.2 Adverse events causing study withdrawal at 0 to 24 hours	3	130	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.27, 7.39]

**Table 2:  
IV lidocaine versus other analgesics**

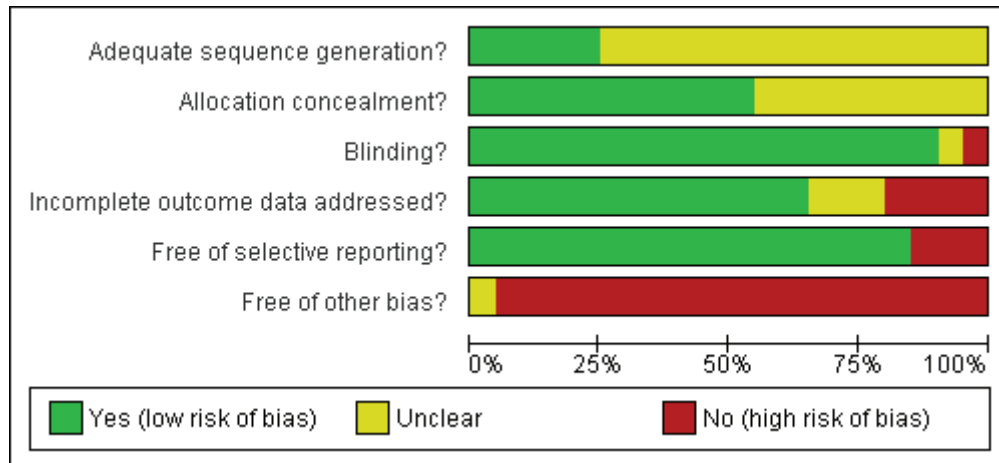
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Mean post-treatment VAS scores	8	339	Mean Difference (IV, Random, 95% CI)	3.79 [-6.87, 14.46]
2.1.1 VAS same day	6	243	Mean Difference (IV, Random, 95% CI)	-1.96 [-9.31, 5.40]
2.1.2 VAS at 1 to 6 days after	1	66	Mean Difference (IV, Random, 95% CI)	0.92 [-9.59, 11.44]
2.1.7 VAS at 12+ months	1	30	Mean Difference (IV, Random, 95% CI)	28.00 [20.00, 36.00]
2.2 Other summary measures of continuous pain intensity or pain relief	4	145	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.29, 0.39]
2.2.1 Maximum % reduction in pain VAS from baseline (same day)	1	59	Std. Mean Difference (IV, Fixed, 95% CI)	-0.49 [-1.01, 0.03]
2.2.2 Mean "pain relief" VAS	1	38	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.47, 0.80]
2.2.7 Ordinal scale pain intensity	2	48	Std. Mean Difference (IV, Fixed, 95% CI)	0.80 [0.15, 1.45]
2.3 Rates of clinically significant pain relief	5	252	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.37, 1.03]
2.3.1 Pain reduction > 30%	2	63	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.23, 1.95]
2.3.2 Pain reduction > 50%	4	189	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.33, 1.08]
2.4 Rates of adverse events	8	298	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.28, 2.98]
2.4.1 Mild-to-moderate events	8	256	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.27, 3.62]
2.4.2 Events causing study withdrawal	1	42	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.26]

**Figure 1**

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Attal 2000	?	+	+	+	-	-
Attal 2004	+	+	+	?	+	-
Barnowsky 1999	?	?	+	+	+	-
Catala 1994	?	?	-	?	+	-
Finnerup 2005	+	+	+	+	+	-
Galer 1996	+	+	+	-	-	-
Gormsen 2009	+	+	+	-	+	-
Gottrup 2006	?	+	+	+	+	-
Kastrup 1987	?	?	+	-	+	?
Kvarnstrom 2003	?	+	+	+	+	-
Kvarnstrom 2004	?	+	+	+	+	-
Lemming 2005	?	+	+	+	-	-
Marchettini 1992	?	?	+	+	+	-
Medrik-Goldberg 1999	?	?	+	+	+	-
Rowbotham 1991	?	?	+	+	+	-
Sorenson 1995	?	?	+	?	+	-
Tremont-Lukats 2006	+	+	+	+	+	-
Wallace 1996	?	?	?	+	+	-
Wallace 2000	?	?	+	+	+	-
Wu 2002	?	+	+	-	+	-

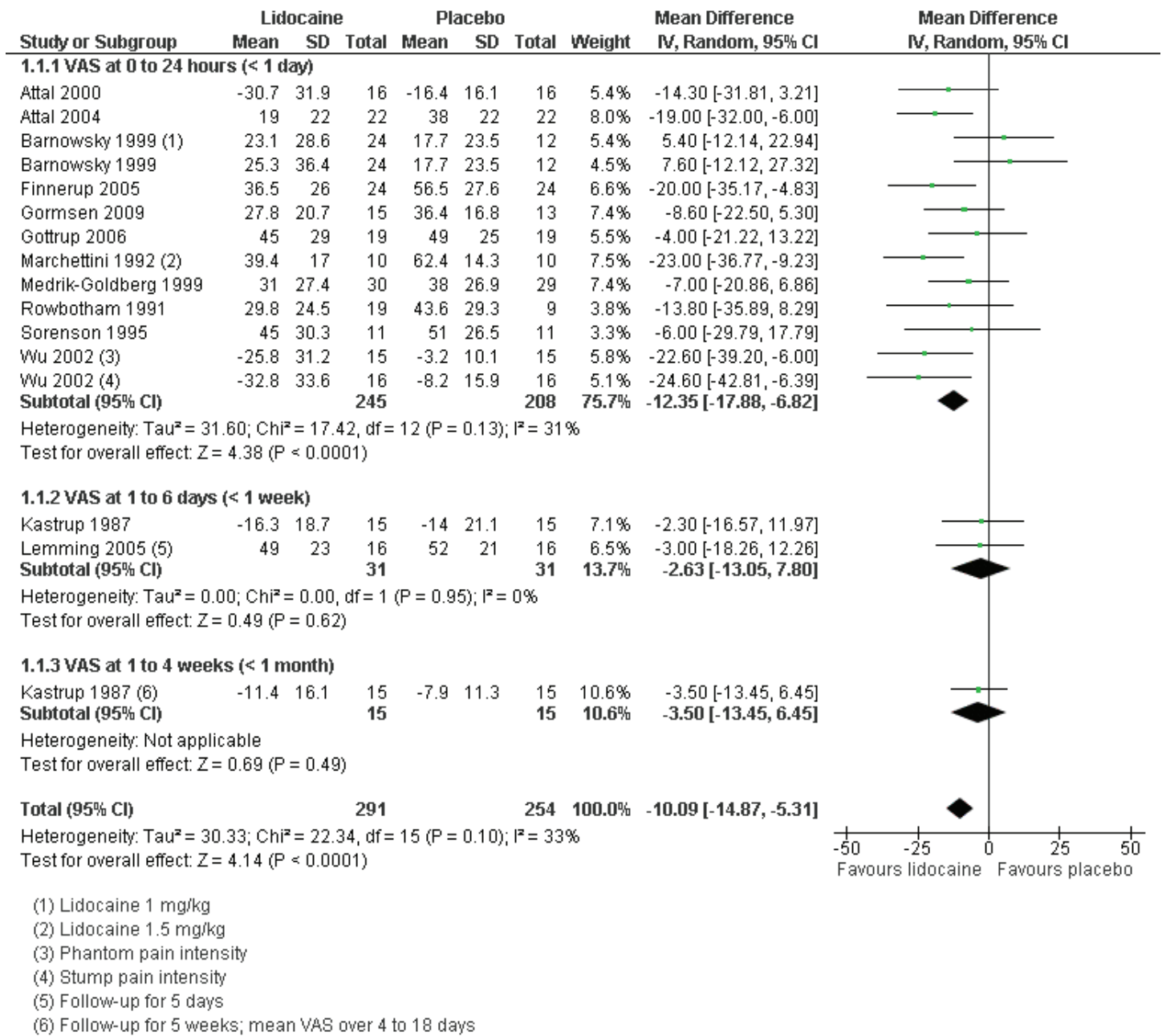
**Methodological quality summary: Review authors' judgments about each methodological quality item for each included study**

**Figure 2**



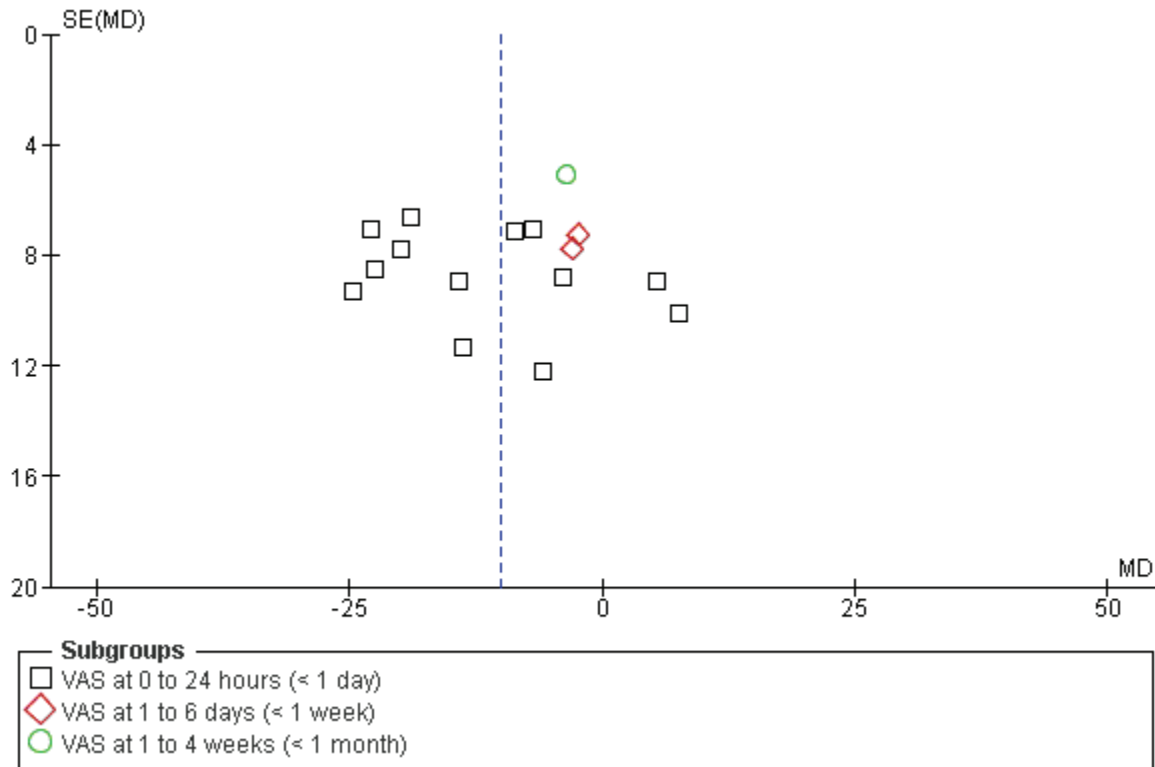
**Methodological quality graph: Review author's judgments about each methodological quality item presented as percentages across all included studies**

**Figure 3. Analysis 1.1**



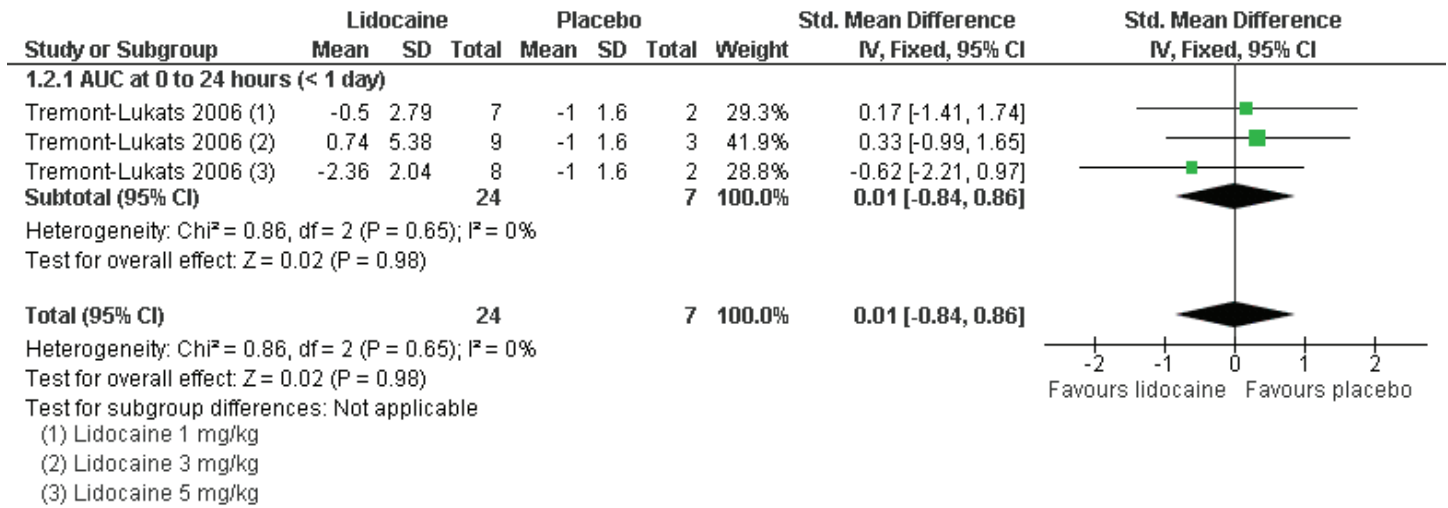
**Forest plot of Comparison 1 – Lidocaine versus placebo or inactive control, Outcome 1.1 – Mean post-treatment VAS or VAS-change scores**

**Figure 4. Analysis 1.1**



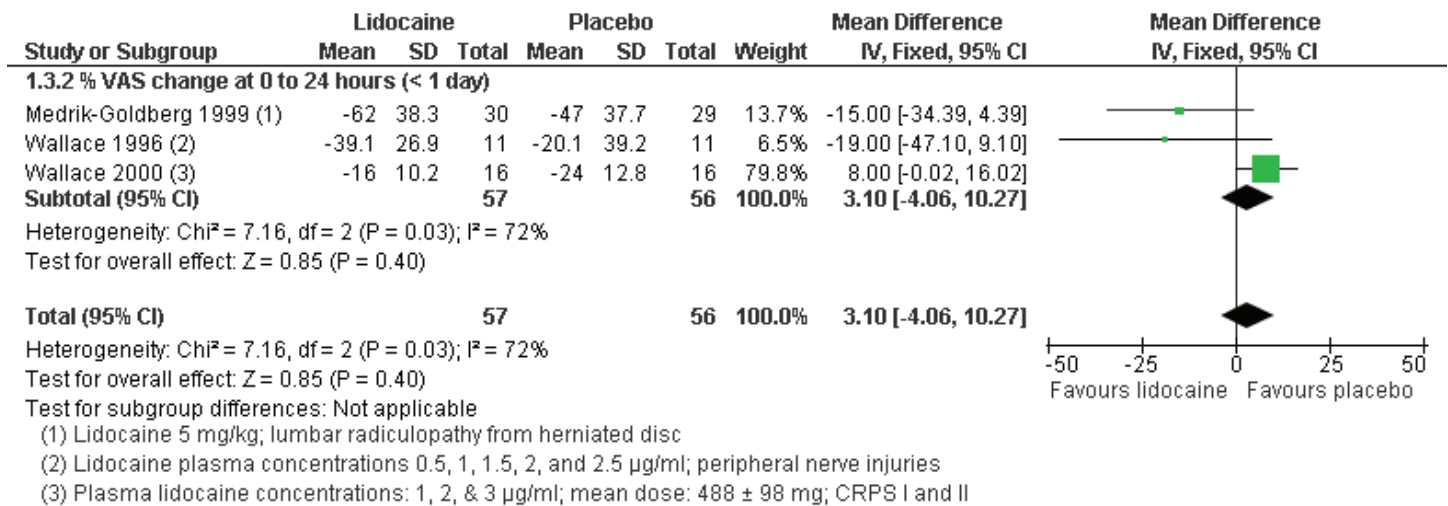
**Funnel plot of Comparison 1 – Lidocaine versus placebo or inactive control,  
Outcome 1.1 – Mean post-treatment VAS or VAS-change scores**

**Figure 5. Analysis 1.2**



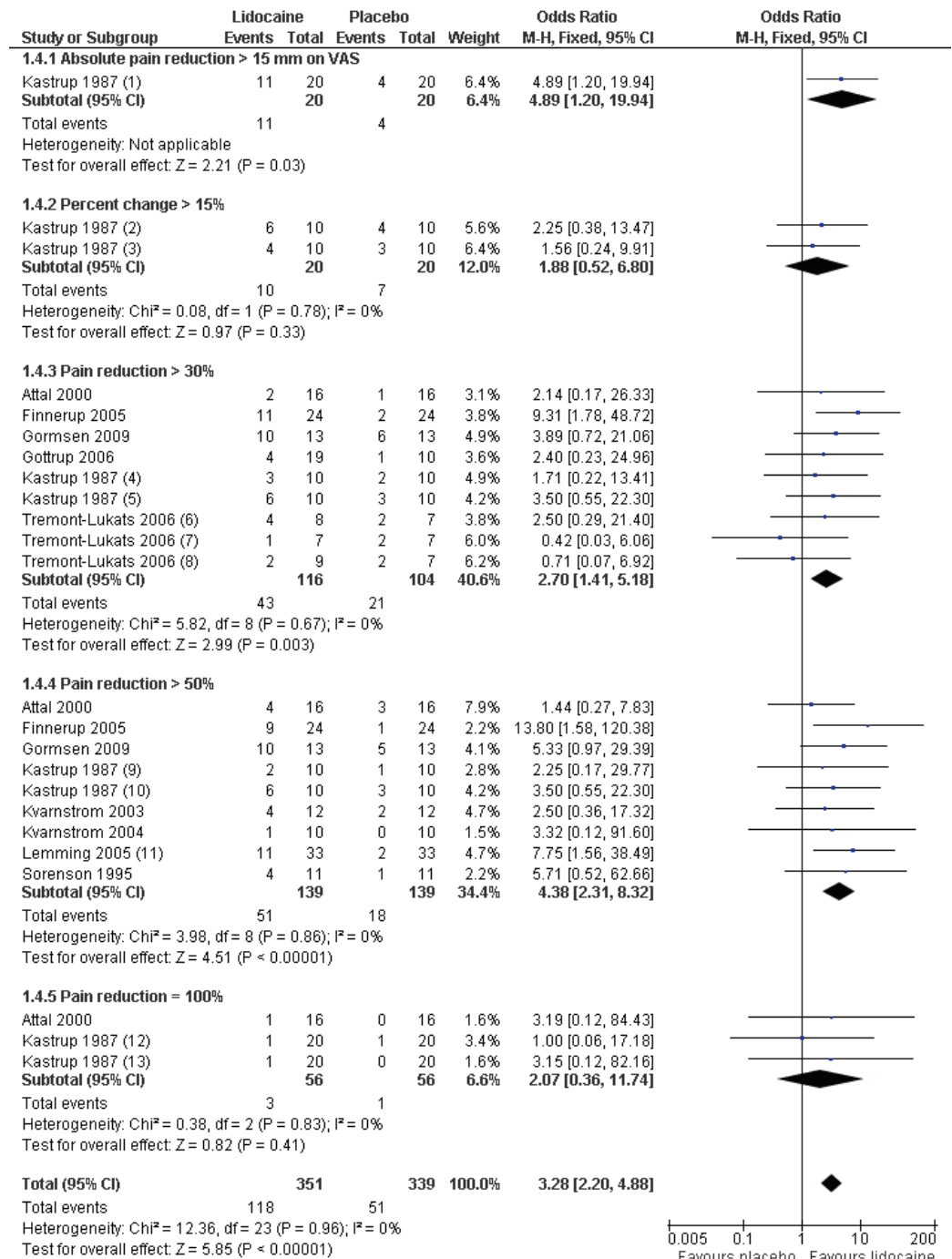
**Forest plot of Comparison 1 – Lidocaine versus placebo or inactive control,  
Outcome 1.2 – Mean area under the VAS-versus-time curve**

**Figure 6. Analysis 1.3**



**Forest plot of Comparison 1 – IV lidocaine versus placebo or inactive control,  
Outcome 1.3 – Mean percent change in baseline VAS**

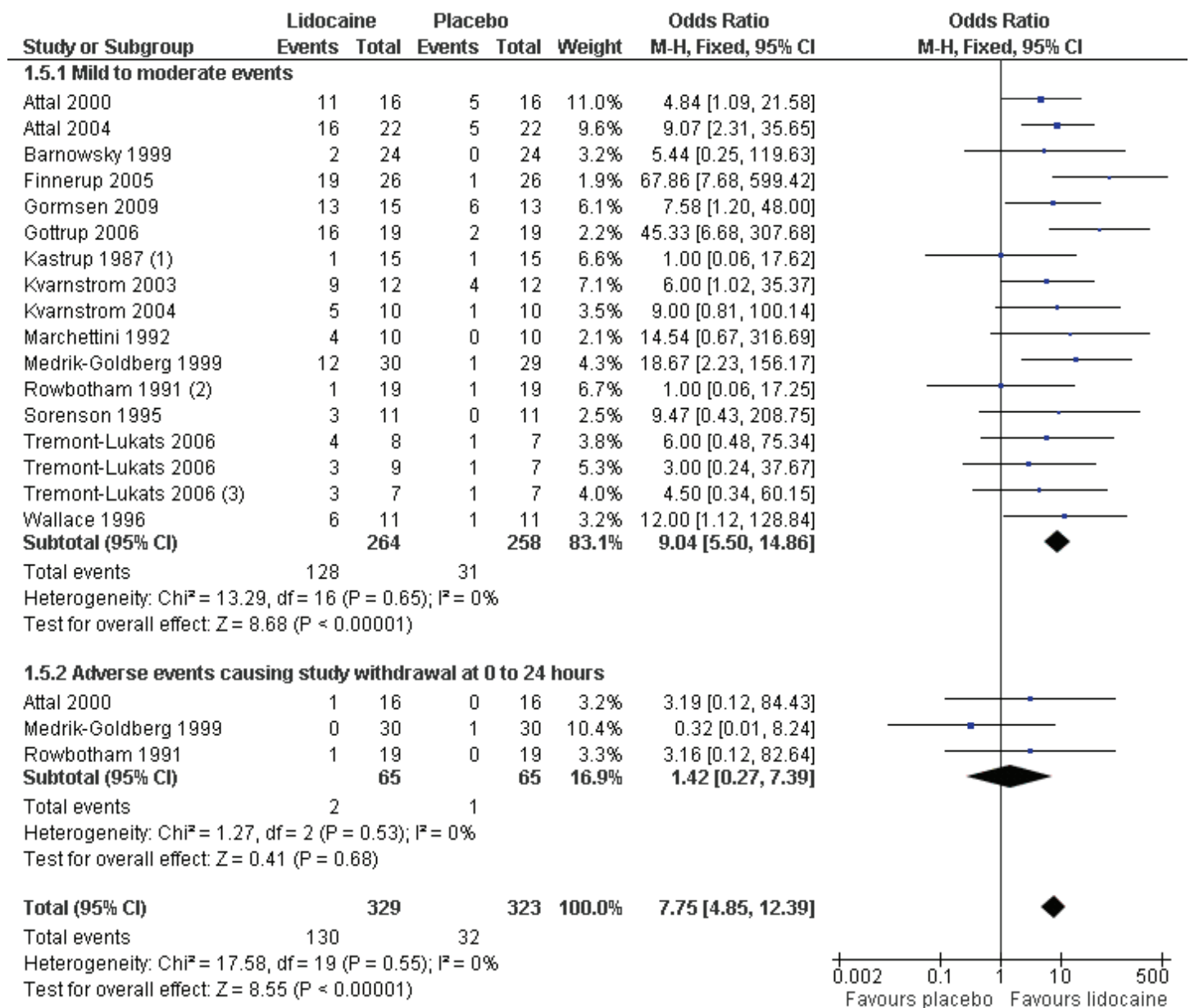
**Figure 7.**  
**Analysis 1.4**



- (1) Follow-up for 5 weeks; outcome at 3 days
- (2) Outcome at 3 days; adjusted sample sizes; original event rates: 11/20 lidocaine, 9/20 placebo.
- (3) Outcome at 18 days; adjusted sample sizes; original event rates: 7/20 lidocaine, 4/20 placebo.
- (4) Outcome at 18 days; adjusted sample sizes; original events rates: 5/20 lidocaine, 4/20 placebo.
- (5) Outcome at 3 days; adjusted sample sizes; original events rates: 11/20 lidocaine, 6/20 placebo
- (6) Lidocaine 5 mg/kg; parallel study; unadjusted sample sizes.
- (7) Lidocaine 1 mg/kg; unadjusted sample sizes.
- (8) Lidocaine 3 mg/kg; unadjusted sample sizes.
- (9) Outcome at 18 days; adjusted sample sizes; original event rates: 3/20 lidocaine, 2/20 placebo.
- (10) Outcome at 3 days; adjusted sample sizes; original event rates: 11/20 lidocaine, 6/20 placebo
- (11) Follow-up period: 5 days
- (12) Outcome at 18 days; "0" cells in both groups replaced by "1", otherwise, samples unadjusted.
- (13) Outcome at 3 days; unadjusted sample sizes due to small event rates.

**Forest plot of Comparison 1 - Lidocaine versus placebo or inactive control,  
Outcome 1.4 – Clinically significant pain relief by response rates**

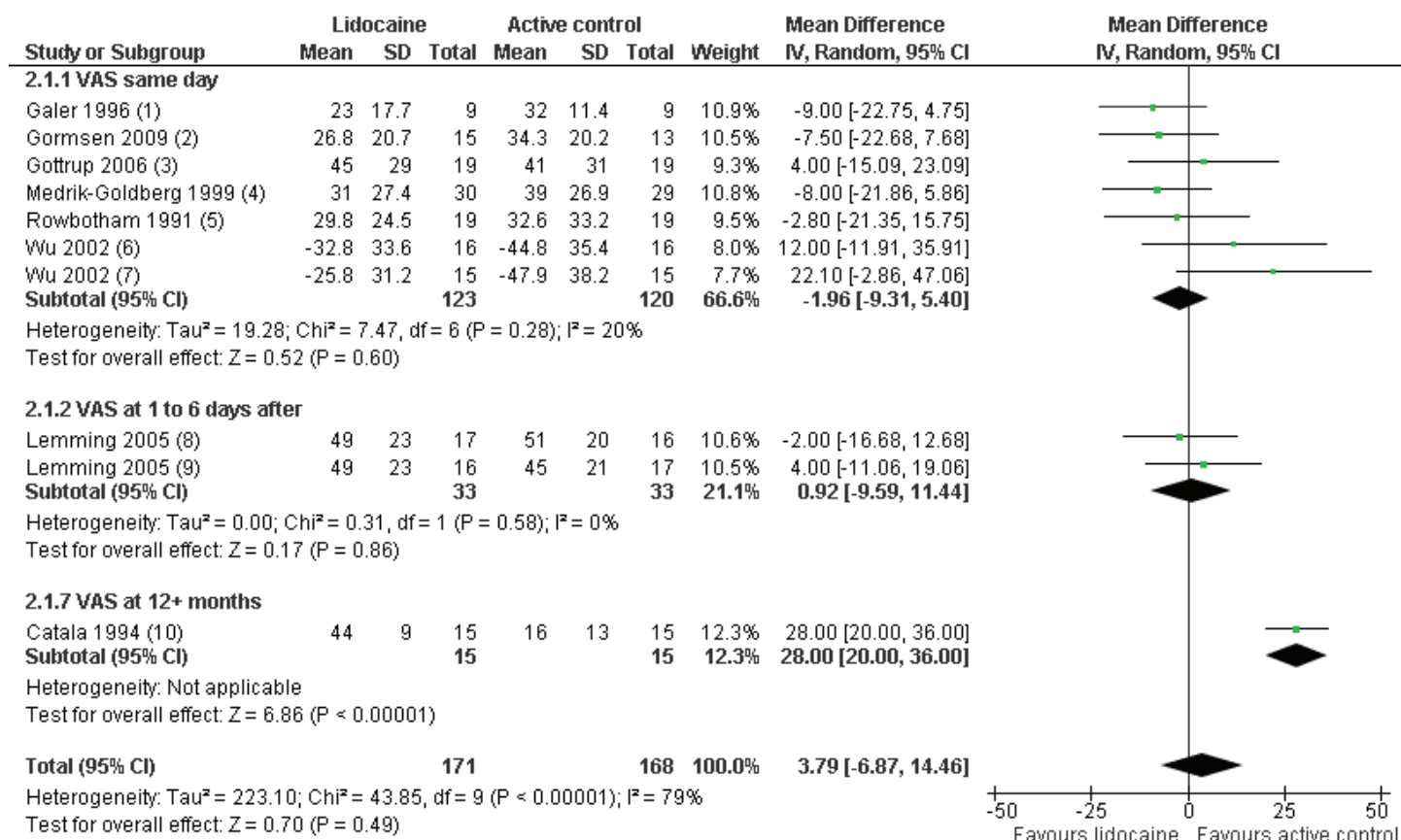
**Figure 8. Analysis 1.5**



- (1) "0" numerator cells replaced by "1" in both groups
- (2) "0" numerator cells replaced by "1" in both groups
- (3) Four-arm parallel study design comparing IV lidocaine at 1, 3, and 5 mg/kg to placebo. No adjustment for shared comparison

**Forest plot of Comparison 1 – Lidocaine versus placebo or inactive control,  
Outcome 1.5 – Adverse events**

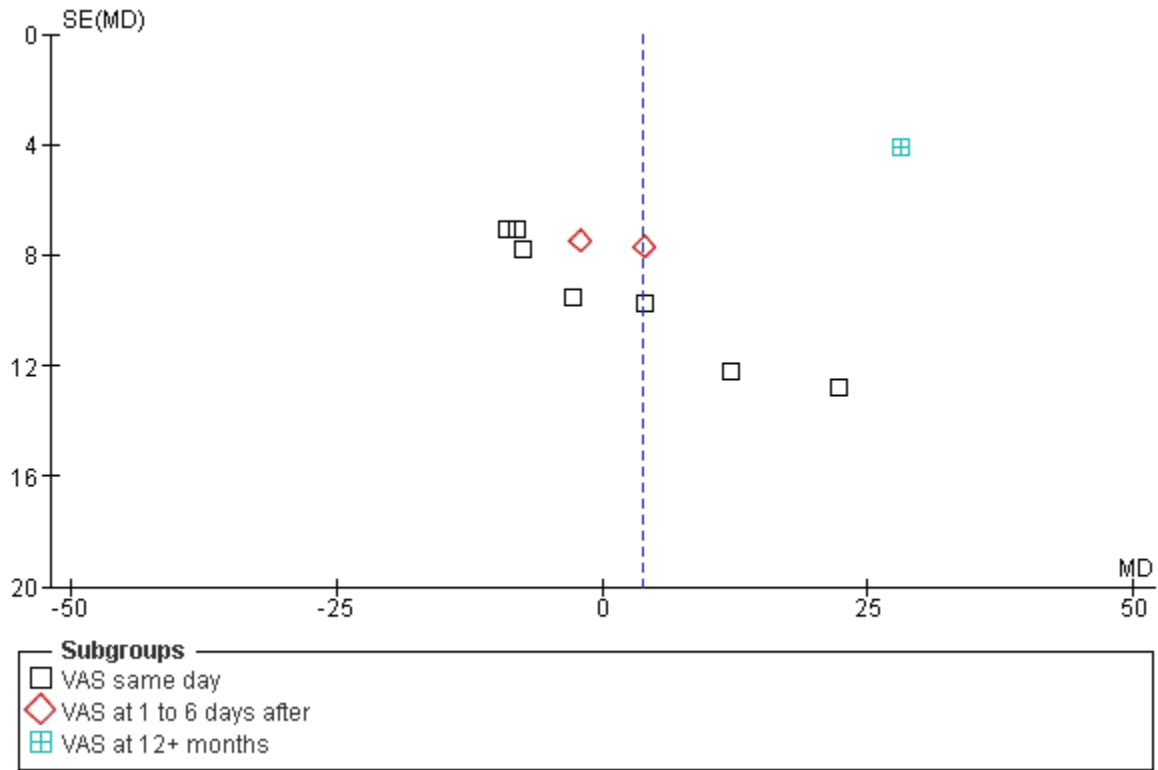
**Figure 9. Analysis 2.1**



- (1) Lidocaine 5 mg/kg vs 2 mg/kg
- (2) Lidocaine 5 mg/kg vs NS1209 (AMPA antagonist)
- (3) Lidocaine 5 mg/kg vs ketamine 0.24 mg/kg
- (4) Lidocaine 5 mg/kg vs amantadine 2.5 mg/kg
- (5) Lidocaine 5 mg/kg vs morphine 0.3 mg/kg
- (6) Lidocaine 5 mg/kg vs morphine 0.25 mg/kg for phantom pain
- (7) Lidocaine 5 mg/kg vs morphine 0.25 mg/kg for stump pain
- (8) Lidocaine 5 mg/kg vs morphine 0.3 mg/kg
- (9) Lidocaine 5 mg/kg vs ketamine 0.3 mg/kg
- (10) Lidocaine 3 mg/kg vs sympathetic block; parallel design; follow-up at 1 year.

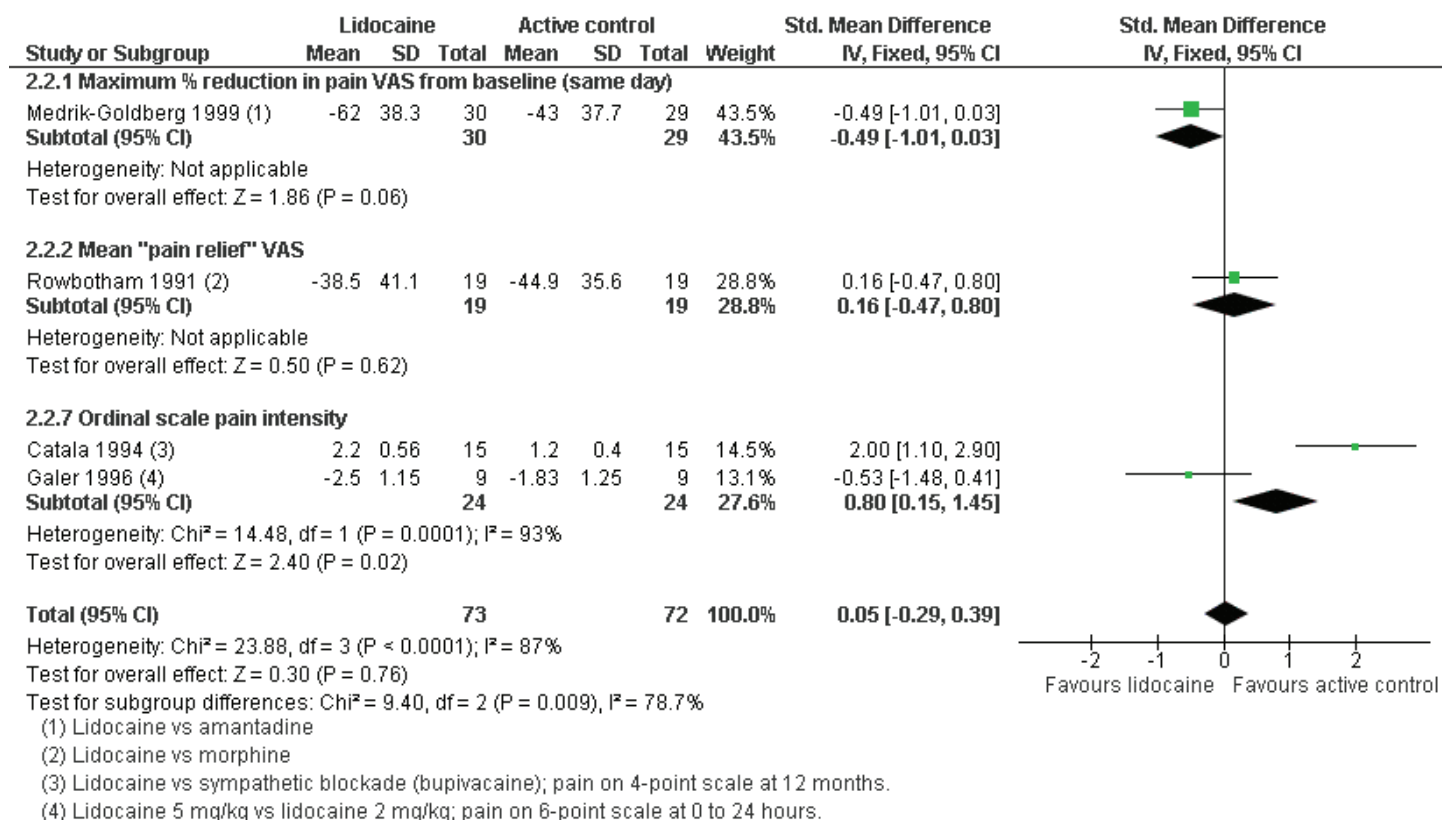
**Forest plot of Comparison 2 – Lidocaine versus active control, Outcome 2.1 – Mean post-treatment VAS or VAS change scores**

**Figure 10. Analysis 2.1**



**Funnel plot of Comparison 2 – Lidocaine versus active control,  
Outcome 2.1 – Mean post-treatment VAS or VAS change scores**

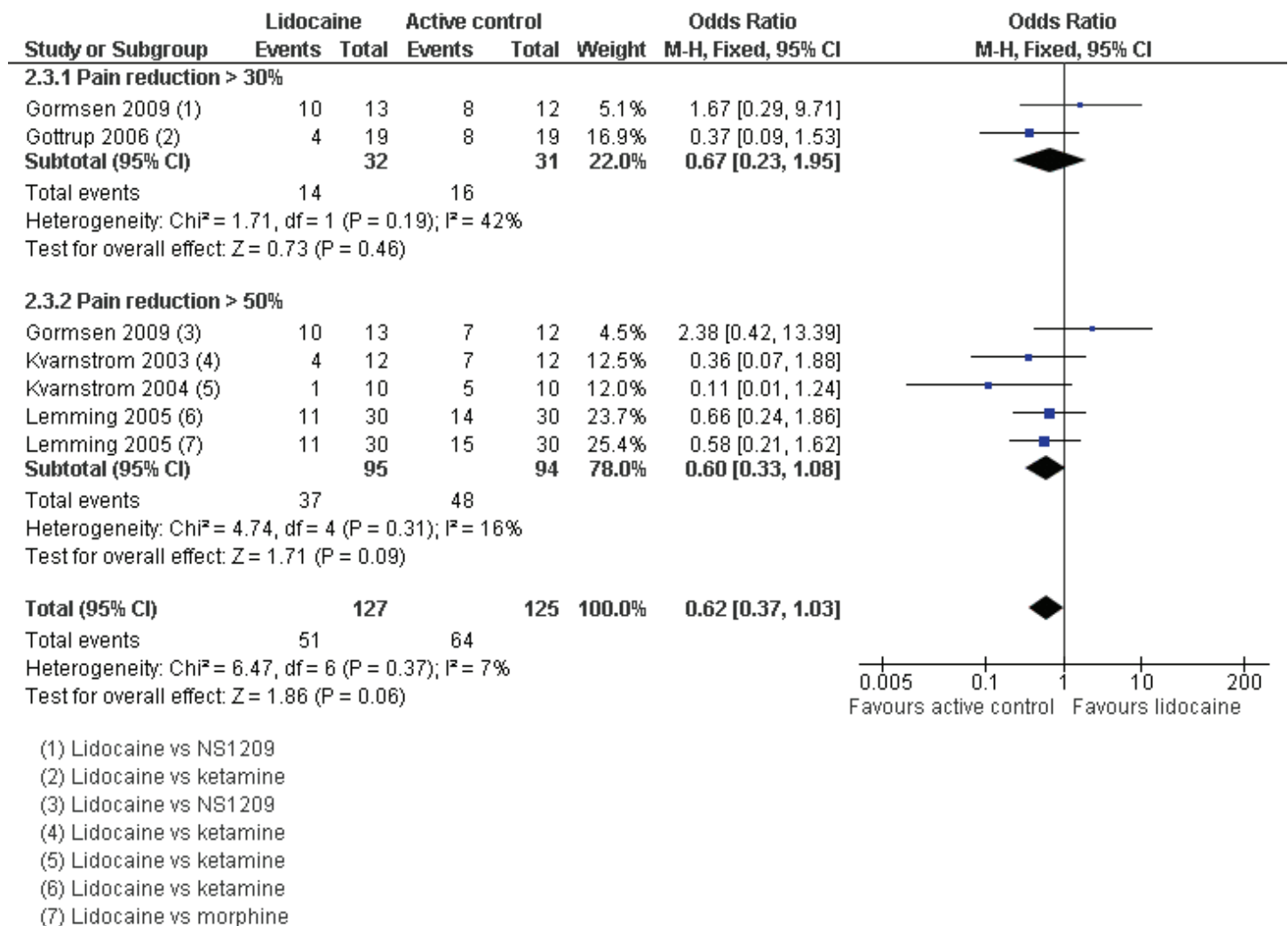
**Figure 11. Analysis 2.2**



**Forest plot of Comparison 2 – Lidocaine versus active control,**

**Outcome 2.2 – Other VAS-based summary measures**

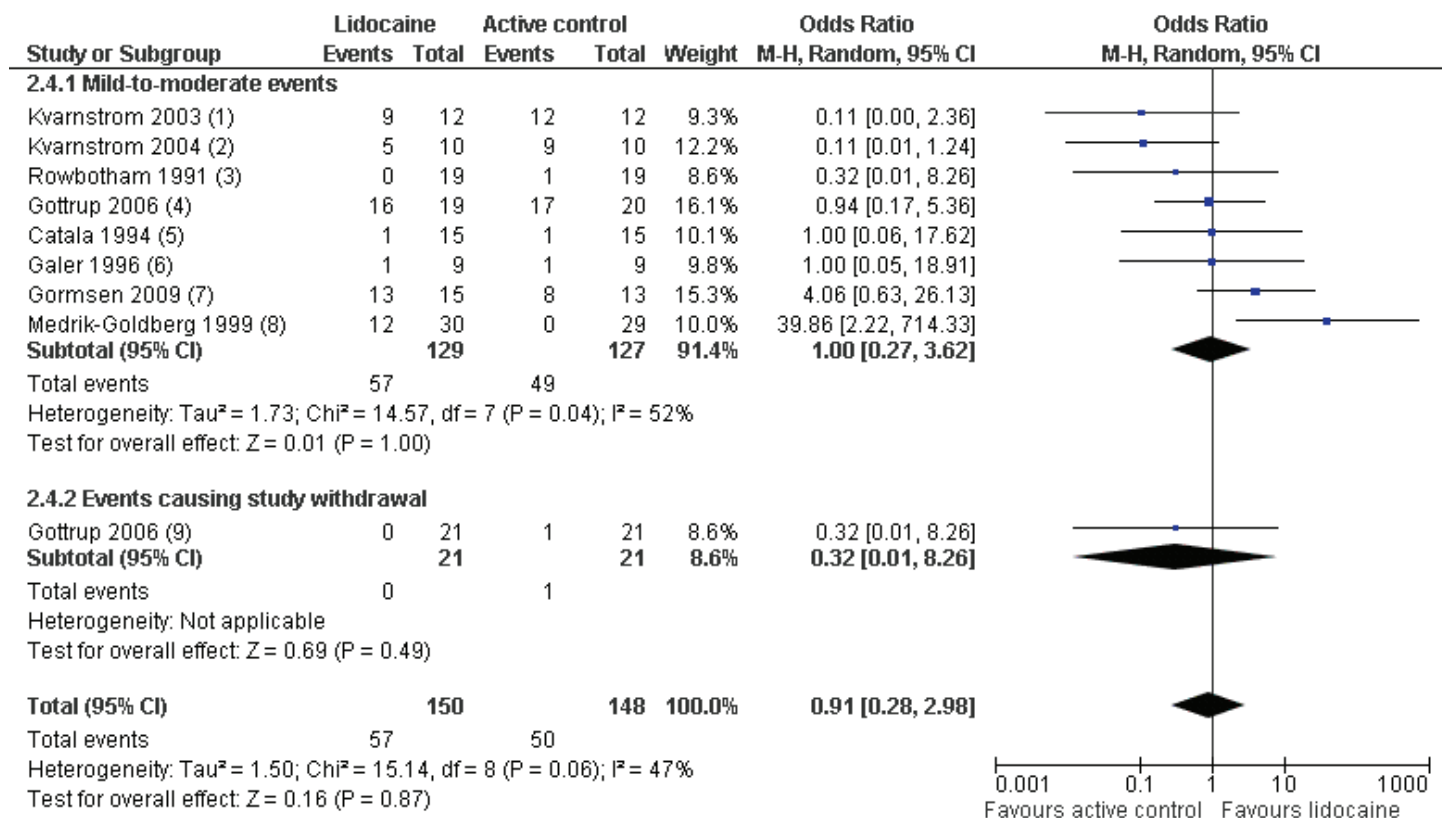
**Figure 12. Analysis 2.3**



**Forest plot of Comparison 2 – Lidocaine versus active control,**

**Outcome 2.3 – Significant pain relief by response rates**

**Figure 13. Analysis 2.4**



(1) Lidocaine 2.5 mg/kg vs ketamine 0.4 mg/kg

(2) Lidocaine 5 mg/kg vs ketamine 0.4 mg/kg

(3) vs morphine

(4) vs ketamine 0.1 mg/kg

(5) vs bupivacaine; '0' cells in both comparison groups replaced by '1'.

(6) Lidocaine 5 mg/kg versus lidocaine 2 mg/kg; '0' cells in both comparisons groups replaced by '1'.

(7) vs NS1209.

(8) vs amantadine

(9) vs ketamine 0.1 mg/kg.

**Forest plot of Comparison 2 – Lidocaine versus active control,**

**Outcome 2.5 – Mild to moderate adverse events**