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Systemic administration of local anesthetic agents to relieve neuropathic pain (Review)

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[Intervention Review]

Systemic administration of local anesthetic agents to relieve neuropathic pain

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ABSTRACT

Background

Lidocaine, mexiletine, tocainide, and flecainide are local anesthetics which give an analgesic effect when administered orally or parenterally. Early reports described the use of intravenous lidocaine or procaine to relieve cancer and postoperative pain. Interest reappeared decades later when patient series and clinical trials reported that parenteral lidocaine and its oral analogs tocainide, mexiletine, and flecainide relieved neuropathic pain in some patients. With the recent publication of clinical trials with high quality standards, we have reviewed the use of systemic lidocaine and its oral analogs in neuropathic pain to update our knowledge, to measure their benefit and harm, and to better define their role in therapy.

Objectives

To evaluate pain relief and adverse effect rates between systemic local anesthetic-type drugs and other control interventions.

Search methods

We searched MEDLINE (1966 through 15 May 2004), EMBASE (January 1980 to December 2002), Cancer Lit (through 15 December 2002), Cochrane Central Register of Controlled Trials (2nd Quarter, 2004), System for Information on Grey Literature in Europe (SIGLE), and LILACS, from January 1966 through March 2001. We also hand searched conference proceedings, textbooks, original articles and reviews.

Selection criteria

We included trials with random allocation, that were double blinded, with a parallel or crossover design. The control intervention was a placebo or an analgesic drug for neuropathic pain from any cause.

Data collection and analysis

We collected efficacy and safety data from all published and unpublished trials. We calculated combined effect sizes using continuous and binary data for pain relief and adverse effects as primary and secondary outcome measurements, respectively.

Main results

Thirty-two controlled clinical trials met the selection criteria; two were duplicate articles. The treatment drugs were intravenous lidocaine (16 trials), mexiletine (12 trials), lidocaine plus mexiletine sequentially (one trial), and tocainide (one trial). Twenty-one trials were crossover studies, and nine were parallel. Lidocaine and mexiletine were superior to placebo [weighted mean difference (WMD) = -11; 95% CI: -15 to -7; P < 0.00001], and limited data showed no difference in efficacy (WMD = -0.6; 95% CI: -7 to 6), or adverse effects

versus carbamazepine, amantadine, gabapentin or morphine. In these trials, systemic local anesthetics were safe, with no deaths or life-threatening toxicities. Sensitivity analysis identified data distribution in three trials as a probable source of heterogeneity. There was no publication bias.

Authors' conclusions

Lidocaine and oral analogs were safe drugs in controlled clinical trials for neuropathic pain, were better than placebo, and were as effective as other analgesics. Future trials should enroll specific diseases and test novel lidocaine analogs with better toxicity profiles. More emphasis is necessary on outcomes measuring patient satisfaction to assess if statistically significant pain relief is clinically meaningful.

PLAIN LANGUAGE SUMMARY

Systemic administration of local anesthetic agents to relieve neuropathic pain

Intravenous lidocaine and oral derivatives relieve pain from damage to the nervous system (neuropathic pain). In early reports, intravenous lidocaine and its oral analogs mexiletine and tocainide relieved neuropathic pain, a type of pain caused by disease in the nervous system. However, the evidence was conflicting. The authors reviewed all randomized studies comparing these drugs with placebo or with other analgesics and found that: local anesthetics were superior to placebo in decreasing intensity of neuropathic pain; limited data showed no difference in efficacy or adverse effects between local anesthetics and carbamazepine, amantadine, gabapentin or morphine; local anesthetics had more adverse effects than placebo; and local anesthetics were safe.

BACKGROUND

Lidocaine (lignocaine) is a local anesthetic used intravenously as an antiarrhythmic drug. Early reports described the use of intravenous lidocaine or procaine to relieve cancer and postoperative pain (Keats 1951; Gilbert 1951; De Clive-Lowe 1958; Bartlett 1961). Interest reappeared decades later when patient series and clinical trials reported that parenteral lidocaine and its oral analogs tocainide, mexiletine, and flecainide relieved neuropathic pain in some patients (Boas 1982; Lindblom 1984; Petersen 1986; Dunlop 1988; Bach 1990; Awerbuch 1990).

The International Association for the Study of Pain defined neuropathic pain as pain resulting from damage to the peripheral or central nervous system (Merskey 1994). There is no uniform classification for neuropathic pain, but a convenient and simple anatomical classification divided neuropathic pain as peripheral or central, depending on the location of the primary lesion (Bowsher 1991; Dworkin 2003). This classification attempted to give uniformity to a symptom that represented the common expression of many different disorders. There is experimental evidence that systemic lidocaine lessened pain by blockade of peripheral and central sodium ion gate channels (Woolf 1985), although the analgesic action of lidocaine may be more complex, and the inhibition of neuronal ectopic discharges is one of several mechanisms involved (Nagy 1996).

It is unclear why some patients with neuropathic pain responded better to lidocaine than others (Mao 2000). In animal models, lidocaine modified or relieved some components of neuropathic pain (Abdi 1998), an observation reproduced in clinical studies (Galer 1993; Stracke 1994; Wallace 2000a; Attal 2000; Attal 2004). Lidocaine was not suitable for long term use, so pain clinicians and researchers used its oral analogs, mostly mexiletine. However, the evidence for mexiletine as an effective drug in neuropathic pain was weak; the number of patients needed to treat (NNT) diabetic polyneuropathy or central pain with mexiletine ranged between 10 and 38, placing this drug below other agents for neuropathic pain (Sindrup 1999; Sindrup 2000). This estimate was based on a few trials providing response rates, when most trials measured pain relief as continuous data. A systematic review of local anesthetic drugs for chronic (including neuropathic and nociceptive) pain concluded that lidocaine and oral analogs "are effective in pain due to nerve damage, but there is little or no evidence to support their use in cancer-related pain" (Kalso 1998). Kalso 1998 included in his review other types of pain, and did not measure the therapeutic benefit of lidocaine and its oral analogs. With the recent publication of clinical trials with high quality standards, we have reviewed the use of systemic lidocaine and its oral analogs in neuropathic pain to update our knowledge, to measure their benefit and harm, and to better define their role in therapy.

OBJECTIVES

1. To evaluate whether lidocaine and its oral analogs are beneficial in decreasing chronic neuropathic pain.
2. To estimate the treatment effect of local anesthetics compared with placebo or other analgesic drugs.
3. To quantify the safety of systemic local anesthetics.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled clinical trials with random allocation, double blind, with parallel or crossover design comparing systemically administered lidocaine or its oral analogs (mexiletine, tocainide, and flecainide) with placebo or with any other active treatment.

Types of participants

Patients of any age with neuropathic pain from:

- painful peripheral neuropathy regardless of etiology;
- plexopathy or radiculopathy of unknown, traumatic, infectious, toxic, or infiltrative origin;
- complex regional pain syndrome type I (reflex sympathetic dystrophy), and II (causalgia);
- central pain from cerebrovascular lesions or tumors;
- spinal cord injuries;
- multiple sclerosis and other demyelinating diseases;
- trigeminal neuralgia;
- post-amputation pain;
- fibromyalgia.

Types of interventions

The interventions included will be Lidocaine or its analogs given parenterally or orally, compared with placebo or any active treatment including other analgesics, acupuncture, TENS, biofeedback, relaxation techniques, regional blockade, anticonvulsants, antidepressants, or spinal cord stimulation. Since topical formulations of lidocaine have limited systemic absorption, we excluded studies of topical lidocaine.

Types of outcome measures

- Intensity of spontaneous pain or its relief, measured by any validated measurement tool.
- Adverse effects, defined as any untoward symptom due to lidocaine or its analogs with enough intensity to cause study withdrawal or to decrease the dose of the drug. The type of adverse effect reported in the trials are listed in the table of included studies.

Search methods for identification of studies

We used a search strategy based on guidelines published elsewhere (Lefebvre 2001). We combined a series of search terms relevant to randomized double blind, placebo-controlled trials with pain-specific terms and with the subject headings related to forms of local anesthetic agents or to local anesthetics as a class of drugs. The search strategy was adapted to each of the following databases: The Cochrane Central Register of Controlled Trials (1st Quarter 2004); EMBASE (January 1980 to December 2002); MEDLINE (January 1966 to May 2004); CancerLit (1963 to December 2002); LILACS; and the System for Information on Grey Literature in Europe (SIGLE). We searched in CancerLit and SIGLE for conference proceedings. We contacted investigators to learn about unpublished trials, or to request additional information on published trials. There was not any language restriction. We

adapted the list of terms found in Appendix 1 to each of the electronic databases.

Data collection and analysis

Three of us independently screened all titles and abstracts identified in the literature search. We resolved any disagreement by discussion to find a consensus, and were not blinded to the author names, affiliated institutions, journal of publication, or study results. We examined the internal validity of each trial using the Oxford Quality Score criteria (Jadad 1996).

Assessment of methodological quality

1. Was the study randomized? (1 = yes; 0 = no)
2. Was the method of randomization adequate and well described? (0= not described; 1= described and adequate; -1= described, but not adequate)
3. Was the study described as double blind? (1= yes; 0 = no)
4. Was the method of double blinding adequate and well described? (0 = not described; 1 = described and adequate; -1 = described, but not adequate)
5. Was there a description of withdrawals and dropouts sufficient to determine the number of patients in each treatment group entering and completing the trial? (1 = yes; 0 = no)

Each trial received a score of 0 to 5 points, with higher scores indicating a higher methodological quality.

Data collection and analysis

We extracted data on participants, methods, interventions, outcome measurements, and adverse effects from the original articles. The outcomes and the instruments to measure them varied across studies. The outcome measurements were published as binary (dichotomous) or continuous data. The continuous data included medians, means with standard deviations or standard errors. In the articles that did not publish standard deviations, we could still derive the standard deviation if the article included the number of participants and the standard error. We dichotomized ordinal scales to pain relief (proportion of patients with significant and total pain relief) or no pain relief (moderate, mild, or no pain relief) to estimate response rates. We extracted data on adverse effects as listed and defined by the authors. We did not make judgments on drug causation. We combined the data on pain relief and adverse effects to obtain a pooled effect size for each outcome.

Synthesis and presentation of data

Data analysis was done with RevMan Analyses for Windows version 1.0.2, the analysis module for RevMan 4.2.2. We estimated the weighted mean difference (WMD) between placebo control or active control and the treatment intervention using visual analog scores (VAS). We studied statistical heterogeneity using the Cochrane Q test (Chi^2) and the I^2 statistics. The I^2 statistic is a reliable and robust test to quantify heterogeneity, since it does not depend on the number of trials or on the between-study variance. I^2 measures the extent of inconsistency among the studies' results, and we can interpret this statistic as the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. Other sensitivity tests to investigate heterogeneity and publication bias were the comparison between model effects (fixed and random), and subgroup analyses by number of participants, etiology, drug type, trial quality, trial design, and time of outcome measurement. We used funnel plots to investigate publication bias and heterogeneity.

For the analysis of response rates and for adverse effects we used binary data to estimate odds ratios (OR) in a random effects model. We included pooled response rates as defined by the different investigators, because such outcomes may have more clinical meaning to patients and clinicians (Farrar 2000; Farrar 2001).

RESULTS

Description of studies

Trial characteristics

(Table: Characteristics of included studies; Table: Characteristics of excluded studies)

Our search identified 1902 titles, of which 44 trials were relevant for this review. We excluded 14 trials (Table: Characteristics of excluded studies); two articles were duplicate publications (Kastrup 1986, Stracke 1992); one study of flecainide was terminated when the drug was removed from the market (Dunlop 1991; CAST 1989); five trials examined the use of intravenous lidocaine in experimentally-induced acute pain in normal volunteers (Rowlingson 1980; Wallace 1997; Ando 2000; Dirks 2000; Gottrup 2000); three trials did not have or describe random allocation (Bach 1990; Reljanovic 1996; Sakurai 1999); two trials were unblinded (Posner 1994; Català1994); and one study was single blinded, without random allocation (Keats 1951).

We included 30 randomized, double blind, controlled clinical trials for chronic neuropathic pain (Attal 2000; Attal 2004; Backonja 2000; Baranowski 1999; Bruera 1992; Chabal 1992; Chiou-Tan 1996; Dejgard 1988; Ellemann 1989; Fassoulaki 2002; Galer 1996; Kastrup 1987; Kemper 1998; Kieburtz 1998; Kvarnstrom 2003; Kvarnstrom 2004; Lindstrom 1987; Marchettini 1992; Matsuoka 1996; Matsuoka 1997; Medrik 1999; Oskarsson 1997; Rowbotham 1991; Stracke 1994; Sörensen 1995; Wallace 1996; Wallace 2000a; Wallace 2000b; Wright 1997; Wu 2002). The treatment intervention was lidocaine in 16 trials, mexiletine in 12 trials, sequential lidocaine and mexiletine in one study (Galer 1996), and tocainide in one study (Lindstrom 1987). The treatment sequence design was parallel in eight trials, and crossover in 22 trials. Two of the crossover trials did not specify washout periods (Lindstrom 1987; Marchettini 1992). Three randomized studies appeared as abstracts (Backonja 2000; Matsuoka 1996; Matsuoka 1997). We retrieved complete information from one of these trials (Backonja 2000). The age (mean +/- standard deviation) of the participants in all included trials was 51.7+/-10.3 years.

Methods of trials included for systematic review

Lidocaine trials

Researchers gave lidocaine intravenously in different doses: 5 mg/kg in nine studies (Attal 2000; Attal 2004; Bruera 1992; Ellemann 1989; Kastrup 1987; Marchettini 1992; Medrik 1999, Rowbotham 1991; Sörensen 1995); 1 and 5 mg/kg in one study (Baranowski 1999), 2 and 5 mg/kg in one study (Galer 1996); a bolus of 1 mg/kg followed by a 4 mg/kg infusion in one study (Wu 2002); 1, 3 and 5 mg/kg infusions in one study (Backonja 2000); and a 1.5 mg/kg bolus only in another study (Marchettini 1992). Two studies infused lidocaine at 2.5 mg/kg over 40 min (Kvarnstrom 2003; Kvarnstrom 2004). Fifteen of the trials included normal saline

as placebo, two studies used diphenhydramine as active placebo (Wallace 2000a; Wu 2002), and five studies included an active control (with or without placebo): morphine sulfate (Rowbotham 1991; Wu 2002), ketamine (Kvarnstrom 2003; Kvarnstrom 2004), or amantadine (Medrik 1999).

One clinical trial randomly allocated participants to receive lidocaine at two different doses followed by mexiletine, but did not have a control intervention (Galer 1996). Five of the fifteen trials did not describe exclusion criteria (Bruera 1992; Galer 1996; Marchettini 1992; Sörensen 1995; Wallace 2000a).
Researchers in the lidocaine trials measured pain intensity or pain relief in minutes (n = 13; median: 120 min, range: 35-600 min), or in weeks (n = 5; median duration: 5 weeks; range: 1-11 weeks). Eight studies enrolled patients with a specific etiology for peripheral neuropathic pain: painful diabetic polyneuropathy (Kastrup 1987), postherpetic neuralgia (Rowbotham 1991; Baranowski 1999), fibromyalgia (Sörensen 1995), neuropathic pain from tumor infiltration (Ellemann 1989; Bruera 1992), lumbosacral radiculopathy from disc herniation (Medrik 1999), and trauma (Kvarnstrom 2003). Five studies enrolled patients with peripheral neuropathic pain who had more than one disease (Attal 2004; Backonja 2000; Marchettini 1992; Wallace 1996; Wallace 2000a). Two studies enrolled only patients with central pain and one disease (Kvarnstrom 2004; Wu 2002), and one trial enrolled patients with central pain from two different diseases (Attal 2000).

All studies included a 0-100 mm VAS or a 0-10-point numerical rating scale (NRS) to measure pain. Other pain measurement tools were the five-item symptom score scale (FIS) (Kastrup 1987), the short form of the McGill Pain Questionnaire (Baranowski 1999), and the pain relief scale (Galer 1996).
Investigators measured plasma lidocaine concentrations in seven trials (Backonja 2000; Baranowski 1999; Galer 1996; Kastrup 1987; Kvarnstrom 2003; Rowbotham 1991; Wallace 2000a), of which one found a relation between concentration and response to pain (Wallace 2000a).

Mexiletine trials

The randomized controlled trials with mexiletine started at 300 mg/day, increasing to the highest dose set in the trial protocol. The dose ranged from 300 mg/day (Matsuoka 1997), to 1200 mg/day (Galer 1996). The median dose for all trials was 600 mg, in three divided doses. One study used 300 and 450 mg/day (Matsuoka 1996); Four studies included a maximum dose of 600 mg/day (Fassoulaki 2002; Kemper 1998; Kieburtz 1998; Wright 1997); in two clinical trials the highest dose was 675 mg/day (Oskarsson 1997; Stracke 1994); 750 mg/day (Chabal 1992), and in one trial the dose was 450 mg/day (Chiou-Tan 1996). One group used a dose of 10 mg/kg/day (Dejgard 1988). All trials included inactive placebo, and two also had active controls, amitriptyline (Kieburtz 1998), and gabapentin (Fassoulaki 2002).

The median duration of mexiletine trials was nine weeks (range: 2-26 weeks). In one trial, some patients remained on the drug for up to a year (Galer 1996). Twelve studies enrolled participants with peripheral neuropathic pain: nine of these trials included patients with a single diagnosis, such as painful diabetic polyneuropathy (Dejgard 1988; Matsuoka 1996; Matsuoka 1997; Oskarsson 1997; Stracke 1994; Wright 1997), HIV-related painful polyneuropathy (Kemper 1998; Kieburtz 1998), and breast cancer patients with postmastectomy pain 3 months after breast surgery (Fassoulaki 2002). Three trials enrolled patients with different diseases (Chabal 1992; Galer 1996; Wallace 2000b). There was only one trial with central pain which enrolled patients with spinal cord injury (Chiou-Tan 1996). In most mexiletine trials, the investigators measured pain with a VAS or a NRS except one trial that used the Gracely Pain Scale (Kieburtz 1998). Other instruments used were the FIS (Dejgard 1988), the McGill Pain Questionnaire (Chiou-Tan 1996; Stracke 1994), and a categorical pain scale (Matsuoka 1996; Matsuoka 1997).
Four of the 13 trials did not describe exclusion criteria (Dejgard 1988; Galer 1996; Matsuoka 1996; Matsuoka 1997). Researchers measured plasma mexiletine levels in five studies (Dejgard 1988; Oskarsson 1997; Kieburtz 1998; Wallace 2000b; Fassoulaki 2002). None of these studies found a association between plasma levels and pain relief.

Tocainide trial

The only randomized controlled trial with tocainide tested this drug against carbamazepine for idiopathic trigeminal neuralgia (Lindstrom 1987). The dose of tocainide was 20 mg/kg divided daily in three doses. The authors rated pain daily on an 11-point NRS, and measured outcomes the last 10 days of a 2 week treatment with each drug. This trial specified exclusion criteria. The authors measured tocainide concentrations in plasma, but did not investigate a relation between concentration and pain relief.

Risk of bias in included studies

Twelve clinical trials (40%) were of good methodological quality, scoring 4 points (Bruera 1992; Chabal 1992; Chiou-Tan 1996; Medrik 1999; Wallace 2000b; Attal 2000; Backonja 2000) or 5 points (Attal 2004; Wright 1997; Kieburtz 1998; Fassoulaki 2002; Wu 2002). Eighteen trials (60%) scored 2 points (Kastrup 1987; Matsuoka 1996; Matsuoka 1997) or 3 points (Kvarnstrom 2003; Kvarnstrom 2004; Lindstrom 1987; Dejgard 1988; Ellemann 1989; Rowbotham 1991; Marchettini 1992; Sörensen 1995; Galer 1996; Wallace 1996; Oskarsson 1997; Kemper 1998; Baranowski 1999; Wallace 2000a; Stracke 1994). The median score was 3 points for all trials with either lidocaine or its oral analogs.

Of the 30 trials in this review, 10 (33%) described a method for random allocation (Kvarnstrom 2003; Kvarnstrom 2004; Attal 2004; Bruera 1992; Chabal 1992; Wright 1997; Kieburtz 1998; Backonja 2000; Wu 2002; Fassoulaki 2002); six (20%) described sample size calculations (Chiou-Tan 1996; Wright 1997; Kieburtz 1998; Medrik 1999; Wu 2002; Fassoulaki 2002), and 11(37%) described the blinding method (Attal 2004; Ellemann 1989; Bruera 1992; Oskarsson 1997; Kieburtz 1998; Medrik 1999; Attal 2000; Backonja 2000; Wallace 2000b; Wu 2002; Fassoulaki 2002). Of these studies with a description of the blinding method, five had a strategy to ensure that patients were blinded throughout the study (Attal 2000; Attal 2004; Backonja 2000; Wallace 2000b; Wu 2002). The number of participants receiving lidocaine or oral analogs varied but in general was small; the median number of participants for all trials was 28 (range: 8-87 participants).

Effects of interventions

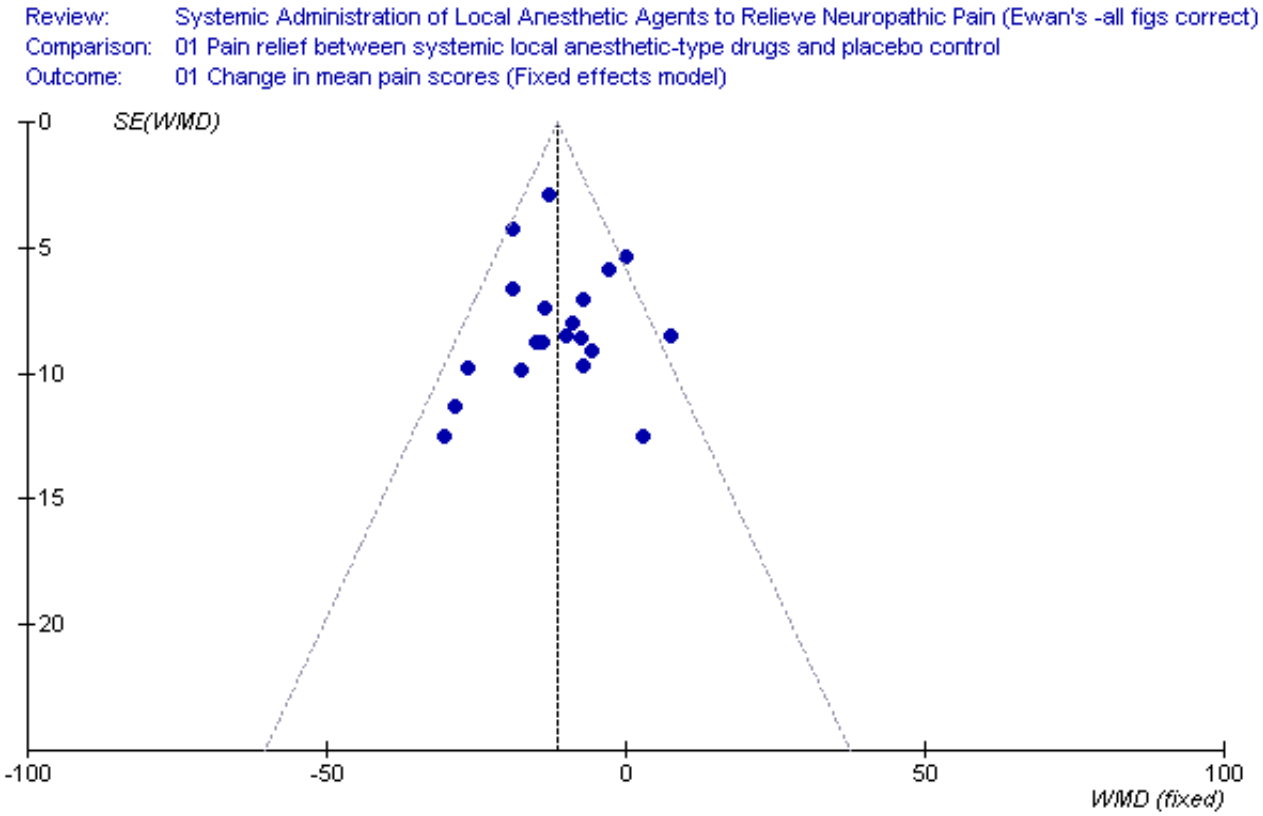
Relief of spontaneous pain with intravenous lidocaine or oral mexiletine versus placebo (comparison 01, outcome 01)

We computed into the meta-analysis all the placebo-controlled trials with lidocaine and mexiletine that published continuous

data on pain relief, excluding five trials because such data were unavailable (Ellemann 1989; Kvarnstrom 2003; Kvarnstrom 2004; Sörensen 1995), or because of a different scale (Kieburtz 1998). For trials using more than one dose of lidocaine or mexiletine, we selected the highest dose. For trials measuring pain at different times we chose the last measurement time, except one study in which we pooled the data from all time points (Bruera 1992). However, the negative results of this study were not affected by data from any single time point. We pooled daytime and nocturnal pain scores for one trial (Oskarsson 1997), and for a trial on post-amputation pain evaluating stump and phantom pain, we chose stump pain (Wu 2002).

Pretreatment and posttreatment mean pain scores were available from 11 lidocaine and nine mexiletine trials (n = 750), for a total of 371 patients allocated to the treatment drug and 379 patients allocated to the placebo intervention. The summary effect size favors both lidocaine and mexiletine over placebo to decrease chronic neuropathic pain in the random and fixed effects models (WMD = -11 mm; 95% CI: -15 to -7 mm; P <0.00001, random effects model). We found a slightly asymmetric funnel plot due to three studies on or out of the 95% confidence intervals (Figure 1, Stracke 1994; Baranowski 1999; Fassoulaki 2002).

Figure 1. Funnel plot of comparison 01, outcome 01. The trials by Baranowski, Fassoulaki and Stracke are on or outside the 95% confidence intervals.



Meta-analysis of lidocaine trials vs. placebo (comparison 01, outcome 01)

In the lidocaine trials, 187 patients received lidocaine and 186 patients received placebo. Lidocaine was superior to placebo (WMD = -11 mm; 95% CI: -17 to -5 mm, P = 0.0003). Heterogeneity was very small.

Meta-analysis of mexiletine trials vs. placebo (comparison 01, outcome 01)

In the mexiletine clinical trials included for meta-analysis, 184 patients received mexiletine and 193 received placebo. The heterogeneity was greater than in the lidocaine trials because two trials had a wide dispersion of data around the mean (Stracke 1994; Fassoulaki 2002). The combined effect size also favored mexiletine over placebo (WMD = -11 mm; 95% CI: -16 to -6 mm, P < 0.0001).

Lidocaine or mexiletine vs. placebo, binary data with response rates (Comparison 01, outcome 02)

We could extract response rates from 14 trials (lidocaine, n = 9; mexiletine, n = 5). Each article included presented a proportion of responders, most defining response as a 30% or greater decrease in pain. The total number of participants was 589, 321 patients treated with local anesthetics and 268 patients who received placebo. Forty-seven percent (151/321) allocated to local anesthetics had significant pain relief compared with 22% (59/268) of those receiving placebo (OR: 3.4, 95% CI: 2.1 to 5.6). Mexiletine was as effective as lidocaine for patients with significant pain relief, and the studies with mexiletine yielded more precise estimates of

effect mainly because of the number of participants. There was no evidence of significant heterogeneity.

Subgroup analyses

Sample size (comparison 02, outcome 01)

We divided trials in two subgroups: fewer than 25 participants (n = 17, six mexiletine trials and 11 lidocaine trials), and more than 25 participants (n = 3, two mexiletine trials and one lidocaine trial). The subgroup of trials with fewer than 25 patients was not statistically heterogeneous, despite mixing lidocaine and mexiletine trials and that 50% of these studies were negative. There was evidence of heterogeneity in the subgroup with more than 25 patients due to one trial (Stracke 1994). These results suggest that heterogeneity was not due to the intervention or to the number of participants, and that there was no publication bias because half of the small trials were negative studies.

Time of outcome measurement (comparison 02, outcomes 02, 03, and 04)

Although there was no indication of statistical heterogeneity in the subgroup with outcome measurements within 24 hours (n = 10, all lidocaine trials), the second subgroup (outcome measurements recorded for more than 24 hours, n = 10) was heterogeneous. If we excluded one trial (Stracke 1994, outcome 03), heterogeneity virtually disappeared (P = 0.41, I^2 = 2.8%). In another sensitivity analysis, we excluded the three trials with widely spread data (Stracke 1994; Baranowski 1999; Fassoulaki 2002, outcome 04); the effect sizes for both subgroups separately or combined showed no evidence of statistical heterogeneity.

Trial design (Comparison 02, outcome 5)

The classification by trial design was straightforward: trials had a crossover or a parallel treatment sequence. There was evidence of heterogeneity in the parallel trials, explained by two studies (Stracke 1994; Fassoulaki 2002). The heterogeneity disappeared if we excluded these trials.

Methodological quality (comparison 02, outcome 06)

We divided trials in three subgroups: studies with a score between two and three points (low and fair quality), four points (good quality), and studies with five points (very good quality). The subgroup with the best methodological quality was homogeneous despite one trial with widely spread data, suggesting that high methodological quality reduced heterogeneity. The heterogeneity present in the other two subgroups decreased sensibly after removing two trials with widely dispersed data. Such findings suggest that heterogeneity is less if trials have very high quality standards.

Etiology (comparison 02, outcome 07)

We divided all trials in six subgroups:

1. Peripheral, metabolic cause: five trials, four with mexiletine and one with lidocaine. All participants had diabetic polyneuropathy.
2. Peripheral, infectious cause: Three trials including HIV-1-related polyneuropathy treated with mexiletine (n = 1), and postherpetic neuralgia treated with lidocaine (n = 2).
3. Peripheral, posttraumatic cause: four trials with mexiletine and lidocaine (two each).
4. Peripheral, cancer: one trial using lidocaine.
5. Peripheral, mixed: three trials using lidocaine.
6. Central/mixed, vascular or posttraumatic causes: three trials included participants with pain due to amputation, stroke, and spinal cord injury. Lidocaine was the treatment drug in two of these trials.

The subgroup with peripheral neuropathic pain from diabetic polyneuropathy showed heterogeneity (Stracke 1994). We could not conclude anything from subgroup 4 (peripheral, cancer), because there is only one trial published to date with continuous data that could be included in the meta-analysis.

Meta-analysis of lidocaine or mexiletine vs. other active treatments (comparison 03, outcome 01)

Five trials (n = 206: 102 treated with lidocaine or analogs, 104 treated with another analgesic) compared the analgesia between local anesthetic-type drugs and carbamazepine (Lindstrom 1987), gabapentin (Fassoulaki 2002), amantadine (Medrik 1999), or morphine (Rowbotham 1991; Wu 2002). There was no evidence of heterogeneity, and no evidence that these drugs were better than lidocaine or its oral analogs to decrease neuropathic pain (WMD = -0.6 mm; 95 % CI: -7 to 6 mm).

Adverse effects

The most common adverse effects were sleepiness, fatigue, nausea, perioral numbness, metallic taste, and dizziness.

Local anesthetic-type drugs and placebo (comparison 04, outcome 01

Twenty-one studies provided rates of adverse effects for placebo and lidocaine or oral analogs (Attal 2004; Dejgard 1988; Ellemann 1989; Fassoulaki 2002, Kvarnstrom 2004; Bruera 1992; Chabal 1992; Marchettini 1992; Stracke 1994; Sörensen 1995; Chiou-Tan 1996; Wallace 1996; Oskarsson 1997; Kemper 1998; Kieburtz 1998; Baranowski 1999; Backonja 2000; Attal 2000; Rowbotham 1991; Wallace 2000b; Wright 1997). Two of these (Bruera 1992; Chiou-Tan 1996) did not find adverse effects to report on participants using the treatment drug or placebo, and were excluded from this analysis. Of 813 participants in the remaining 19 studies, 442 were treated with lidocaine or mexiletine, and 371 received placebo. One hundred fifty-three patients (35%) allocated to lidocaine or mexiletine experienced adverse effects, compared with 44 patients (12%) allocated to placebo (OR = 4.6, 95% CI: 3.0 to 7.0). These results indicate that treatment with lidocaine or mexiletine was significantly associated with more adverse effects than placebo.

Lidocaine and oral analogs versus other analgesics used as active controls (comparison 05, outcome 01)

Five trials provided information on adverse effects in 205 participants, 104 treated with lidocaine or oral analogs, and 101 treated with an active control (Lindstrom 1987; Rowbotham 1991; Kieburtz 1998; Fassoulaki 2002; Kvarnstrom 2004). Thirty-two patients (31%) had adverse effects with lidocaine or its oral analogs, and 31 patients (31%) reported adverse effects with active control drugs (OR: 0.8; 95% CI: 0.2 to 4.0). Based on this data, there is no evidence that treatment with lidocaine or mexiletine was less safe or had more adverse effects than other analgesics

used for neuropathic pain. However, these results are limited by the few trials with adequate information on this outcome, and by the heterogeneity of the model.

DISCUSSION

The main and most solid conclusion of this review is that intravenous lidocaine and its oral analog mexiletine were more effective than placebo in decreasing neuropathic pain. The treatment effect was similar and consistent for both drugs despite clinical variability between trials. These results are more precise than previous estimates of effect published for mexiletine (Sindrup 1999; Sindrup 2000). The role of systemic local anesthetics to treat neuropathic pain was controversial, and difficult to define objectively even in comparison with placebo interventions. The complex nature of neuropathic pain, and the methodological flaws of some clinical trials underlie this fragmentary evidence and lack of definition; more than half of the 29 trials were of low or fair methodological quality, one third did not adequately describe the method for random allocation, and 80% did not estimate the number of participants to have enough statistical power. However, these deficiencies could be due to incomplete reporting of a clinical trial at publication and not to poor methodology, as an observational study showed with randomized controlled trials conducted by the Radiation Therapy Oncology Group (Soares 2004).

A previous systematic review of local anesthetics on chronic pain found evidence to support these drugs, yet the evidence was qualitative (Kalso 1998). Other reviews were narrative (Mao 2000), limited by their own nature and prone to author bias. We approached the problem of fragmented evidence by synthesizing all the quantitative data published so far, and by examining variables that may limit and confuse the interpretation of results. We investigated, identified, and explained sources of heterogeneity in this review. By using subgroup analysis we found that statistical heterogeneity was confined to two or three clinical trials, and that their exclusion did lessen heterogeneity but did not affect the overall treatment effect. Therefore, the final results were robust against statistical heterogeneity or clinical variability.

We observed in the subgroup analysis that lidocaine and mexiletine were more effective for pain from diabetes, trauma, and cerebrovascular disease than for other causes. However, such finding comes from an arbitrary, retrospective classification to assess heterogeneity, and we cannot make firm conclusions based on such results. We also investigated publication bias, a frequent problem limiting the validity of systematic reviews and meta-analyses. We did not find evidence of such bias because positive and negative studies were evenly split in trials with fewer than 25 participants, and the effect sizes between small and large studies were roughly similar.

A more difficult question to answer is whether a mean difference of 11 mm on a 0-100 VAS (or 1.1 on a 0-10 NRS) represents a true clinical difference for patients. For neuropathic pain, we believe that this effect size is clinically relevant. First, most study participants had chronic pain, had been previously treated with other analgesics, and had failed such treatments; hence, this is a group very difficult to treat, and small quantitative differences in these patients are valuable. Second, the response to placebo may render new treatments ineffective if such response is large enough to lessen any statistical difference. Third, the analysis of continuous data from pain scales using means or medians is a mathematical attempt to make a multidimensional, subjective variable like pain more objective. A limitation of the use of mean pain scores is that individual responses may not follow a normal probability distribution but rather a bimodal pattern, in which a mean difference of 11 mm can be a clinical difference for some patients (Farrar 2000). Even in the absence of a bimodal distribution, individual patients may experience a larger response.

One solution to this problem in clinical pain research is the use of binary data, expressing results as response rates. The definition of the smallest decline in pain intensity considered successful or clinically significant by the patient has been explored (Sriwatanakul 1982). Recent research analyzing data from large randomized clinical trials showed that a clinically meaningful difference begins around a 30% reduction in pain intensity, or a 2-point reduction in absolute pain intensity (0-10 scale) (Farrar 2000; Farrar 2001; Cepeda 2003). Two of these studies deserve more comment. The first study analyzed pain response data from 130 patients with cancer-related breakthrough pain treated with oral transmucosal fentanyl citrate in a randomized controlled trial. Two of the scales were absolute pain intensity difference, and the percentage pain intensity difference. Patients defined pain relief as clinically important when they did not have to use another opioid as rescue of the painful episode. The best cut-off points defining clinically important pain relief were a change in the percent pain intensity difference of 33% or greater, and a change in absolute pain intensity difference of 2 points or greater on an 11-point numerical scale (Farrar 2000). A similar analysis of 2724 patients participating in clinical trials with pregabalin yielded identical results. These patients had diabetic neuropathy, osteoarthritis, postherpetic neuralgia, chronic low back pain, and fibromyalgia (Farrar 2001). We collected and analyzed the responder rates published in 14 of the mexiletine and lidocaine trials. We found that both drugs were better than placebo. This result is in agreement with the WMD between oral anesthetics and placebo, suggesting that such a difference is clinically important (comparison 01, outcome 02). This result is valid for our systematic review, and could be cautiously extrapolated to future trials using local anesthetics, but may not be applicable to studies of neuropathic pain using other experimental interventions.

In this review, a limited number of trials did not show a difference in efficacy between lidocaine and its oral analogs and other analgesics for treating neuropathic pain, for example the single study that compared tocainide with carbamazepine did not show a difference between the two drugs. This finding implies that lidocaine and mexiletine may be as good as other analgesics. However, even though it is permissible to use different control interventions in a meta-analysis, each control intervention had few patients, and we cannot generalize these results with enough confidence. This area of research needs development, and we need more controlled clinical trials comparing local anesthetic-type drugs against other analgesics.

We showed in this review that lidocaine and other oral analogs of lidocaine caused more adverse effects than placebo. However, the use of such drugs was safe, as we did not find reports of severe toxicity or life-threatening events, and very few withdrawals. We did not find any difference in the frequency of adverse effects between lidocaine or mexiletine compared with morphine, gabapentin, amantadine, amitriptyline, ketamine, or carbamazepine. The use of

other analgesics makes unblinding more difficult, as all participants are exposed to drugs with the potential to cause side effects. Adverse effects from lidocaine or mexiletine may be more frequent in debilitated patients with poor functional status, for example in participants with advanced cancer or HIV infection, creating the impression of easy toxicity that will bias the study results against the experimental intervention. To avoid such bias, researchers should consider stratification by performance status.

In trials controlled with placebo, a narrow margin between benefit and adverse effects can be a problem to keep participants and researchers blinded to the interventions, because it may unmask the treatment intervention to participants and investigators. Very few trials with lidocaine or its oral analogs used strategies to reduce this unmasking effect, such as using active placebos (Wallace 2000a; Wu 2002), including a checklist of unrelated symptoms to confound participants (Backonja 2000), or asking the participants whether they knew what treatment they received at the end of each intervention (Attal 2000; Attal 2004). This is not surprising because only 2% of 191 randomized clinical trials published in top medical and psychiatry journals assessed blinding in participants and investigators, indicating that lack of blinding assessment is widespread (Fergusson 2004).

As intravenous lidocaine has a very limited role to manage pain in the outpatient population, it is important to plan controlled clinical trials with subcutaneous lidocaine given by pumps with preset dose infusions, or to use mexiletine and newer analogs to treat pain in diseases for which there is little or no evidence, such as trigeminal neuralgia, multiple sclerosis, poststroke central pain, post-amputation pain, or the complex regional pain syndrome types I and II.

Considerable debate surrounds the field of systematic reviews. Some have recommended caution on the potential mis-application of such methods (Feinstein 1997). Others have shown how meta-analyses of low quality trials may produce unreliable estimates of treatment effect (Kjaergard 2001, Lau 1997, Hedges 2001). We believe to have kept these risks to a minimum, by taking special care to investigate bias, methodological quality, and by acknowledging the limits of some results in this review.

AUTHORS' CONCLUSIONS

Implications for practice

The role of lidocaine and its oral analogs to control neuropathic pain was unclear until recently. This lack of definition was due to the multifaceted nature of neuropathic pain, the statistical and clinical heterogeneity of many of the trials, and few study participants. These drugs can relieve pain in selected patients with neuropathic pain, compared with placebo. We found evidence suggesting that this analgesic effect is also clinically important.

Implications for research

There should be greater emphasis on accruing patients with neuropathic pain caused by one disease, with well-structured, consistent trials with active placebos or active drug controls to evaluate the efficacy of local anesthetic-type drugs in the treatment of neuropathic pain from specific etiologies. Future trials should also explore subcutaneous infusions with lidocaine, and move to newer oral analogs with more specificity to sodium channel receptor subtypes and fewer adverse effects. In addition, we recommend that future trials include quality of life or global satisfaction endpoints (Rogers 2000; Turk 2003).

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Andrew Baranowski, M.D., London, UK provided means and standard errors of the means of VAS pain scores for the study cited as Baranowski 1999.

Faye Chiou, M.D., Baylor College of Medicine, Houston, Texas, USA reviewed and verified the absence of side effects from mexiletine in the study cited as Chiou-Tan 1996.

Mark Wallace, M.D., University of California, San Diego, California, USA provided complete information on means, standard deviations of pain scores and adverse effects in the study cited as Wallace 2000b.

Per-Eric Lins, M.D., and Per Oskarsson M.D., Huddinge University Hospital, Karolinska Institute, Stockholm, Sweden supplied mean pain scores and standard errors for daytime and nocturnal pain for the study cited as Oskarsson 1997.

Prabhav Tella, M.B.B.S., M.S., Johns Hopkins University, Baltimore, Maryland, USA provided means and standard deviations of pretreatment and posttreatment pain scores for lidocaine, placebo, and morphine for the study cited as Wu 2002.

Trolsen Nielsen, M.D., Aarhus University, Aarhus, Denmark tried to assist in contacting the principal investigator for additional information regarding study cited as Ellemann 1989.

Didier Boussahira, M.D., PhD (Centre d'Evaluation et de Traitement de la Douleur, Paris, France) gave us additional response rates from study cited as Attal 2004.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Attal 2000

Study characteristics	
Methods	Crossover, with 3-wk washout Placebo - 0.9% saline Oxford Quality Score: 4
Participants	18 (16 evaluable); neuropathic pain from stroke and spinal cord injury
Interventions	Lidocaine: 5 mg/kg x 30 min
Outcomes	Compared with placebo, lidocaine significantly reduced evoked pain at the end of treatment (P<0.05, Median difference = - 30, 95% CI: -50 to 0). Lidocaine did not significantly improve spontaneous pain over placebo (Median difference = - 16.5, 95% CI: -38 to 5). Significant analgesia on spontaneous pain for the first 45 min post-injection. During 3 weeks follow-up, no difference in pain between lidocaine

Attal 2000 *(Continued)*

	and placebo. No statistically significant difference between placebo and lidocaine in mechanothermal detection and pain thresholds. Global assessment of pain: 11/32 patients reported moderate-complete pain relief vs 6/32 with placebo.
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 11/16 Placebo: 5/16; 1/16 stopped lidocaine for somnolence and lightheadedness; 2/16 had dysarthria, somnolence, n/v; and dose of lidocaine was reduced.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Attal 2004

Study characteristics

Methods	Crossover, with 2-wk washout Placebo - 0.9% saline Oxford Quality Score: 5
Participants	24 (22 evaluable); peripheral neuropathic pain (trauma, n=14; PHN, n=8). All patients had spontaneous ongoing pain.
Interventions	Lidocaine 5 mg/kg IV x 30 min.
Outcomes	Spontaneous pain intensity was assessed with 100 mm VAS every 15 min after treatment x 1 h, at 90 min, 120 min, and 6 h. Tactile and thermal allodynia were also investigated. Lidocaine significantly decreased spontaneous ongoing pain starting 30 min after infusion until end of study. Lidocaine also reduced mechanical allodynia and hyperalgesia for up to 120 min. No effect on thermal allodynia/hyperalgesia.
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 16/22 Placebo: 5/22 with placebo. Mean number of side effects (mostly mild to moderate and mainly consisting of lightheadedness, perioral numbness, and garbled speech) was 1.7+/-1.4 for lidocaine and 0.5+/-1 for placebo. Sixteen patients continued treatment with mexiletine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Backonja 2000

Study characteristics

Backonja 2000 *(Continued)*

Methods	Parallel pilot Placebo - 0.9% saline Oxford Quality Score: 4
Participants	32 (31 evaluable); peripheral neuropathic pain
Interventions	Lidocaine at 1, 3, and 5 mg/kg/h IV infusions over 6 h, plus an observation time of 4 h (Total: 10 h)
Outcomes	Overall, no difference between median placebo and lidocaine pain scores. Post-hoc analysis showed that lidocaine 5 mg/kg/h significantly decreased pain scores over placebo at 5 h (P = 0.05), and 10 h (P = 0.009) of iv treatment.
Notes	Adverse events (n/N) - nature; withdrawals: Placebo: 6/7 lidocaine (all doses): 21/23. Median number of adverse events between placebo and lidocaine arms not significantly different; 1/32 withdrawn because no data available for analysis. 2/32 stopped treatment before 6 h because of persisting nausea.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Baranowski 1999

Study characteristics

Methods	Crossover, with 1-wk washout Placebo - 0.9% saline Oxford Quality Score: 3
Participants	24; PHN
Interventions	Lidocaine IV 2-h infusion at 1 and 5 mg/kg
Outcomes	No difference between placebo and lidocaine in reducing spontaneous or evoked pain. Lidocaine at 1 and 5 mg/kg significantly reduced the area of allodynia by 65 and 85%, respectively
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine (5 mg/kg): 2/24 - circumoral paresthesia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bruera 1992

Study characteristics	
Methods	Crossover, with 48-h washout Placebo - 0.9% saline Oxford Quality Score: 4
Participants	10; neuropathic pain from cancer
Interventions	Lidocaine 5 mg/kg IV
Outcomes	Lidocaine no better than placebo. Pain levels not significantly lower than pretreatment scores
Notes	Adverse events (n/N) - nature; withdrawals: No adverse events noted

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Chabal 1992

Study characteristics	
Methods	Crossover with 1-wk washout Placebo capsule Oxford Quality Score: 4
Participants	14 (11 evaluable); peripheral neuropathic pain (idiopathic painful polyneuropathy n=3; other peripheral or cranial nerve injuries, n=8)
Interventions	Mexiletine starting at 150 mg po bid x 3 d, with titration up to 750 mg po/day x 15 days. Once at steady-level, patients were followed on that dose x 4 weeks, tapered in one wk, and switched to alternate treatment
Outcomes	Mexiletine (450 mg/day) significantly reduced pretreatment median pain scores by 15 mm, $P < 0.04$), but not when compared to placebo. Mexiletine (750 mg po/day) significantly improved baseline ($P = 0.01$) and placebo ($P = 0.02$) pain scores by 30 mm each. Comparing mexiletine 750 mg/day with placebo, the difference between means was 26.4, SE difference: 9.87; 95% CI: 5.78 to 46.94. 6/11 of patients had pain relief on mexiletine, 0/11 with placebo. Pain w/ burning quality responded better than other pain types.
Notes	Adverse events (n/N) - nature; withdrawals: Mexiletine: 2/11 - mild nausea No withdrawals.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Chiou-Tan 1996

Study characteristics		
Methods	Crossover with 1-wk washout Placebo capsule Oxford Quality Score: 4	
Participants	15 (11 evaluable); dysesthetic pain from spinal cord injuries	
Interventions	Mexiletine 450 mg po daily	
Outcomes	No difference between mexiletine and placebo	
Notes	Adverse events (n/N) - nature; withdrawals: Adverse events not reported; Withdrawals (4/15): atrial fibrillation (n=1); imprisonment (n=1); noncompliance (n=2).	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dejgard 1988

Study characteristics		
Methods	Crossover with 4-wk washout Placebo capsule Oxford Quality Score: 3	
Participants	16; diabetic neuropathy > 6 months duration	
Interventions	Mexiletine 10 mg/kg/day after titration from 150 mg/day	
Outcomes	mexiletine better than placebo using both scales (P = 0.02 for VAS, P<0.01 for total FIS scores; every subitem in FIS was significantly improved except night exacerbation and sleep disturbances	
Notes	Adverse events (n/N) - nature; withdrawals: Mexiletine: 3/16 Placebo: 0/16	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ellemann 1989

Study characteristics	
Methods	Crossover, with 1-wk washout Placebo - 0.9% saline Oxford Quality Score: 3
Participants	20; neuropathic cancer pain (n=10) polyneuropathy (n=7) plexopathy (n=3)
Interventions	Lidocaine (5 mg/kg) IV
Outcomes	No difference between placebo or lidocaine to reduce allodynia (P = 0.99)
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 1/10 -transient drowsiness

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Fassoulaki 2002

Study characteristics	
Methods	Parallel Placebo capsule; Active - gabapentin Oxford Quality Score: 5
Participants	75 (67 evaluable); breast cancer undergoing mastectomy or lumpectomy with axillary node dissection
Interventions	Mexiletine 600 mg po/day, gabapentin 1200 mg po/day, or placebo divided in three equal doses, x 10 days
Outcomes	Three months postmastectomy: the incidence of postmastectomy pain did not differ among groups (45% with mexiletine, 54% for gabapentin, and 58% for placebo). The burning-type of pain was significantly more frequent in patients treated with placebo (7/24), compared to those who took mexiletine (1/20), or gabapentin (1/22) (P=0.033, Fisher exact test)
Notes	Adverse events (n/N) - nature; withdrawals: Mexiletine: 1/21 - n/v Gabapentin: 0/22 Placebo: 0/24

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Galer 1996

Study characteristics	
Methods	Crossover with 1-wk washout. No control - see "Interventions" Oxford Quality Score: 3
Participants	Nine; diabetic polyneuropathy (n=5), other polyneuropathy (n=1), nerve injury (n=2), and lumbosacral arachnoiditis (n=1)
Interventions	Lidocaine 2 mg/kg, 5 mg/kg IV, x 45 min in separate sessions. After second treatment, mexiletine 300 mg/day with possibility to titrate to 1200 mg/day
Outcomes	Lidocaine infusion rate: Statistically significant decrease in mean pain scores for both lidocaine doses. Mexiletine phase: 5/9 (55%) reported moderate or greater pain relief on pain relief scale.
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 1/9 - weakness after each infusion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kastrup 1987

Study characteristics	
Methods	Crossover, with 5-wk washout Placebo - 0.9% saline Oxford Quality Score: 2
Participants	15; painful diabetic neuropathy
Interventions	Lidocaine 5 mg/kg IV infusion x 30 min
Outcomes	Patients on lidocaine had significantly less pain than those with placebo, using FIS and VAS scores ($P < 0.05$, $P < 0.02$ on days 1 and 8 respectively). Responder rate was 11/15 on lidocaine compared to 4/15 on placebo 3 days after infusions ($P < 0.05$). Duration of pain relief from lidocaine was 14 d using FIS and 3 d using VAS. No correlation between lidocaine plasma levels and treatment effects.
Notes	Adverse events (n/N) - nature; withdrawals: No adverse events reported with placebo or lidocaine.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kemper 1998

Study characteristics	
Methods	Crossover, with 1-wk washout Placebo capsule Oxford Quality Score: 3
Participants	22 (16 evaluable); HIV-1-related painful polyneuropathy
Interventions	Mexiletine up to 600 mg/day x 6 weeks
Outcomes	No difference between placebo and mexiletine (P = 0.76). 31% of patients had less pain compared to 31% of patients when they received placebo. Six patients (38%) did not feel relief with either drug.
Notes	Adverse events (n/N) - nature; withdrawals: Mexiletine: 9/16 - n/v (n=9), other GI toxicity (n=1) Placebo: 5/16 - n/v (n=2), diarrhea (n=2), headache and palpitations (n=1); Mexiletine: dose reduction necessary in 4/16 and discontinuation in 3/16 - rash (n=1) and GI toxicity (n=2). Placebo: discontinued in 1/16 - EKG changes.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kieburtz 1998

Study characteristics	
Methods	Parallel Placebo capsule; Active - amitriptyline Oxford Quality Score: 5
Participants	145 (126 evaluable); HIV-1-related painful polyneuropathy
Interventions	Mexiletine escalating from 150 mg/day to 300 mg po bid, or amitriptyline 100 mg po each evening, with a 4-wk titration phase, followed by a 4-wk maintenance phase and a downward titration period
Outcomes	No difference between placebo, mexiletine, or amitriptyline to improve pain, mood, or QoL. Also, there was no difference in change of analgesic doses. mexiletine mean levels at wk 8 were 0.30+/-0.28 mcg/ml
Notes	Adverse events (n/N) - nature; withdrawals: Mexiletine: 22/48 - n/v (n=10), dizziness (n=1), urinary retention (n=3), other (n=8). Placebo: 6/50 -confusion (n=2), urinary retention (n=1), other (n=3).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Kvarnstrom 2003

Study characteristics	
Methods	Crossover, with 1-wk washout (except one case in whom washout was 2 days) Placebo - 0.9% saline; Active - ketamine Oxford Quality Score: 3
Participants	12; peripheral neuropathic pain (trauma, surgery, compression). Mean duration of pain 5.5 years
Interventions	Ketamine 0.4 mg/kg vs. Lidocaine 2.5 mg/kg (1.0 mg/kg x 10 min, then 1.5 mg/kg x 30 min). Venous blood samples taken at time 0, 15, 30, 45, 60, 120, and 150 min for concentrations of ketamine and lidocaine.
Outcomes	Intensity of spontaneous pain on a 10-cm VAS scale, measured at times 0, 15, 30, 45, 60, 120, and 150 min. Responders defined as those with >50% reduction of pain scores below baseline. Dynamic, static, and thermal sensitivity also evaluated. No difference between lidocaine and ketamine (55% and 34% mean pain reduction, respectively) or between lidocaine and placebo (34% vs. 22% mean pain reduction). Response to treatment was recorded in 7/12 (ketamine), 4/12 (lidocaine), and 2/12 (placebo). No correlation between lidocaine concentration and pain response.
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 29 reports of adverse events Placebo: 11 reports. Actual number of patients reporting any adverse effect not reported (although all 12 in ketamine group experienced somnolence). No dropouts.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Kvarnstrom 2004

Study characteristics	
Methods	Crossover, with at least a 4 day washout. Placebo - 0.9% saline; Active - ketamine Oxford Quality Score: 3
Participants	10; spinal cord injury.
Interventions	Ketamine 0.4 mg/kg vs. lidocaine 2.5 mg/kg (1.0 mg/kg x 10 min, then 1.5 mg/kg x 30 min). Venous blood samples taken at time 0, 15, 30, 45, 60, 120, and 150 min for concentrations of ketamine and lidocaine.
Outcomes	Intensity of spontaneous pain on a 10-cm VAS scale, measured at times 0, 15, 30, 45, 60, 120, and 150 min. Responders were defined as those with >50% reduction of pain scores below baseline scores. Dynamic, static, and thermal sensitivity also evaluated. Mean maximal pain reduction was 38% (ketamine), 10% (lidocaine), and 3% (placebo). No difference between lidocaine and placebo (P = 0.31). Responders: 5/10, 1/10, and 0/10 had significant analgesia with ketamine, lidocaine, and placebo respectively
Notes	Adverse events (n/N) - nature; withdrawals:

Kvarnstrom 2004 *(Continued)*

	ketamine: 9/10 lidocaine: 5/10 placebo: 0/10

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Lindstrom 1987

Study characteristics

Methods	Crossover, washout unclear Active - carbamazepine Oxford Quality Score: 3
Participants	12 (8 evaluable); idiopathic trigeminal neuralgia
Interventions	Tocainide 20 mg/kg tid x 2 weeks or carbamazepine x 2 weeks (dose not stated)
Outcomes	Tocainide as effective as carbamazepine against idiopathic trigeminal neuralgia, significantly decreasing mean pain scores from 75 (baseline) to 33.4 (Difference between means: 41.6; 95% CI: 19.1 to 64.1; P = 0.0015). One patient did not have any pain scores to compare.
Notes	Adverse events (n/N) - nature; withdrawals: Tocainide: 3/11 -nausea (n=1), paresthesias (n=1), and skin rash that prompted discontinuation of the drug (n=1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Marchettini 1992

Study characteristics

Methods	Crossover, washout not reported Placebo - 0.9% saline Oxford Quality Score: 3
Participants	10; peripheral neuropathic pain. In 7 patients pain was related to surgery.
Interventions	Lidocaine 1.5 mg/kg over 1 min
Outcomes	10/10 patients had pain relief to lidocaine that lasted up to 35 min. Mean pretreatment VAS: 64.10; Mean 15-min posttreatment VAS: 16.90 (P < 0.001). At 35 min, there was no statistically significant dif-

Marchettini 1992 *(Continued)*

	ference between placebo and lidocaine. Mild pain reduction w/ placebo in 1/10 patients. Disappearance of allodynia in 6/6 patients.
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 4/10 -lightheadedness; No withdrawals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Matsuoka 1996

Study characteristics

Methods	Parallel Placebo capsule Oxford Quality Score: 2
Participants	169; diabetic polyneuropathy
Interventions	Mexiletine 100 mg po tid, mexiletine 150 mg po tid
Outcomes	Responder rate was 35%, 38%, and 21% in patients taking mexiletine 300 mg/day, 450 mg/day, and placebo, respectively. Information on this trial taken from the mexiletine review by Jarvis & Coukell. Based on the data presented in table IV of that review, combined responder rate to mexiletine was 36.4%, 20% for placebo (Difference: 16%, 95% CI: 1.4% to 28.5%)
Notes	Adverse events (n/N) - nature; withdrawals: No mention of adverse events

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Matsuoka 1997

Study characteristics

Methods	Parallel Placebo capsule Oxford Quality Score: 2
Participants	118 (111 evaluable); diabetic polyneuropathy
Interventions	Mexiletine 100 mg po tid x 2 weeks

Matsuoka 1997 *(Continued)*

Outcomes	Mexiletine was better than placebo at the end of 1st wk (42% vs. 17.4%, p < 0.05) and at the 2nd wk (53% vs. 20%, P < 0.05)
Notes	Adverse events (n/N) - nature; withdrawals: No mention of adverse events, toxicity, or withdrawals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Medrik 1999

Study characteristics

Methods	Crossover, with 2 to 7-day washout Placebo - 0.9% saline; Active - amantadine Oxford Quality Score: 4
Participants	30; painful lumbosacral radiculopathy, confirmed by neuro-imaging: L4-L5 (n=15); L5-S1 (n=14); L3-L4 (n=7); and L2-L3 (n=2). Six patients had multi-level involvement
Interventions	Lidocaine 5 mg/kg or amantadine 2.5 mg/kg IV x 2 h
Outcomes	Spontaneous pain: lidocaine was significantly better than placebo or amantadine to relieve pain at 30 (P < 0.05), 120, and 180 min (P < 0.01 for both time points). Evoked pain: lidocaine significantly better than placebo or amantadine to reduce evoked pain (P<0.05).
Notes	Adverse events (n/N) - nature; withdrawals: 24/30 patients reported adverse events: 37 total events with lidocaine and 3 with placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Oskarsson 1997

Study characteristics

Methods	Parallel Placebo capsule Oxford Quality Score: 3
Participants	126 (115 evaluable); painful diabetic neuropathy
Interventions	Mexiletine 225 mg, (group I); 450 mg (group 2); 675 mg (group III) po tid.

Oskarsson 1997 *(Continued)*

Outcomes	No difference between three different mexiletine doses and placebo for day time pain (P = 0.15); mexiletine 675 mg/day significantly better than placebo to relieve nocturnal pain and sleep disturbances (P = 0.03 and P = 0.046, respectively). No significant correlation between plasma concentration, analgesic effect, or adverse events. There was no change in consumption of analgesics.
Notes	Adverse events (n/N) - nature; withdrawals: Mexiletine: 15/84 Placebo: 2/31

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rowbotham 1991

Study characteristics

Methods	Crossover, with 48-h washout Placebo - 0.9% saline; Active - morphine Oxford Quality Score: 3
Participants	19; PHN for > 3 months
Interventions	Lidocaine: target dose = 5 mg/kg IV vs. IV morphine
Outcomes	Both lidocaine and morphine were significantly better than placebo (P = 0.04 and P = 0.02, respectively). Lidocaine not different than morphine.
Notes	Adverse events (n/N) - nature; withdrawals: Withdrawals: 1/19 on lidocaine

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Stracke 1994

Study characteristics

Methods	Parallel Placebo capsule Oxford Quality Score: 3
Participants	95; diabetic neuropathy
Interventions	Mexiletine 450-675 mg po daily

Stracke 1994 *(Continued)*

Outcomes	Overall, no difference between mexiletine and placebo to relieve pain (P = 0.06; 95% CI: -8.6 to 0.2), but mexiletine seemed to be more effective than placebo with stabbing, heat, burning, or formication during the run-in phase of the study. Also, there was no difference in acetaminophen use between placebo and mexiletine
Notes	Adverse events (n/N) - nature; withdrawals: Mexiletine: 11/46 (only with 675 mg/day) Placebo: 6/48

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sörensen 1995

Study characteristics

Methods	Crossover, with 1-wk washout Placebo - 0.9% saline Oxford Quality Score: 3
Participants	12; fibromyalgia
Interventions	Lidocaine 5 mg/kg IV x 30 min
Outcomes	Pain intensity was significantly reduced during infusion and 15 min after infusion in the lidocaine group (P < 0.05 in both cases). No difference between placebo and lidocaine was seen in tender points, muscle strength of hip flexors and handgrip, or endurance. A significant increase in strength of wrist dorsiflexors noted in the lidocaine group (P = 0.03).
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 3/12 -nausea and perioral numbness (n=2), drowsiness, dysarthria, and tremor (n=1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Wallace 1996

Study characteristics

Methods	Crossover, with 1-wk washout Placebo - 0.9% saline Oxford Quality Score: 3
Participants	11; neuropathic pain from peripheral nerve injury

Wallace 1996 *(Continued)*

Interventions	Lidocaine IV infusions targeted to deliver plasma concentrations of 0.5, 1.0, 1.5, 2.0 and 2.5 mcg/ml
Outcomes	lidocaine caused a statistically significant reduction in pain scores compared with placebo (P < 0.05) at concentrations >= 1.5 mcg/ml (between 35 min and 50 min of infusion). There was also a significant reduction in the area of mechanical allodynia, as compared with placebo (P<0.05)
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 7/11 - lightheadedness (n=6), nausea (n=1) Placebo: 1/11 -lightheadedness

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Wallace 2000a

Study characteristics

Methods	Crossover, with 1-wk washout Placebo - diphenhydramine IV Oxford Quality Score: 3
Participants	16; complex regional pain syndrome, types I and II
Interventions	Lidocaine IV infusions targeted to deliver plasma concentrations of 1.0, 1.5, 2.0 and 3.0 mcg/ml or diphenhydramine 70-80 mg
Outcomes	lidocaine caused a statistically significant reduction in cool-evoked pain in the allodynic areas at all three concentration levels, but not with spontaneous pain, or pain evoked by hot, stroking, or von Frey's hairs
Notes	Adverse events (n/N) - nature; withdrawals: Actual numbers of patients reporting adverse events not reported. Mean lightheadedness score higher in lidocaine group than placebo (P < 0.05). Sedation and dry mouth scores similar between groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Wallace 2000b

Study characteristics

Methods	Crossover, with 1-wk washout Placebo capsule Oxford Quality Score: 4

Wallace 2000b *(Continued)*

Participants	20; peripheral neuropathic pain: CRPS I/II (n=10), idiopathic polyneuropathy(n=3), diabetic polyneuropathy(n=1), PHN (n=3), nerve root injury (n=1).
Interventions	Mexiletine starting at 150 mg po bid titrated up to 300 mg po tid over 10 days
Outcomes	18/20 patients tolerated mexiletine 900 mg/day. Peak plasma mexiletine levels were 0.54 mcg/ml. There was no significant effect on area of allodynia, spontaneous pain (P = 0.06), or evoked pain, except stroke-evoked pain by day 10. Plasma levels did not correlate with daily pain scores. Overall, there was no effect of treatment on QoL except on one subitem of the CSQ and the WHYS
Notes	Adverse events (n/N) - nature; withdrawals: Mexiletine: 12/20 - non-GI (trismus, headache, agitation, nightmares, and tremors) (n=11), nausea and sedation (no rates given). Placebo: 4/20

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Wright 1997

Study characteristics

Methods	Parallel Placebo capsule Oxford Quality Score:5
Participants	31 (29 evaluable); peripheral diabetic neuropathy
Interventions	Mexiletine titrated over four days to 200 mg po tid
Outcomes	The authors found no difference between placebo and mexiletine to reduce mean pain scores, (16.5 mm, 95% CI: -7.1 to 40.2 mm, P = 0.19). FIS scores and proportion of patients with relevant relief (a decrease in pain scores > 20 mm, 8/14 in the mexiletine group and 7/15 in the placebo group) were not statistically different.
Notes	Adverse events (n/N) - nature; withdrawals: Lidocaine: 7/15 Placebo: 3/14; Withdrawals: 6/31 (4 from adverse events, 2 from placebo, and 2 from mexiletine).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Wu 2002

Study characteristics	
Methods	Crossover, with 24-h washout Placebo - diphenhydramine IV; Active - morphine IV Oxford Quality Score: 5
Participants	32 (31 evaluable); postamputation pain: stump pain alone (n=11) phantom pain alone (n=9), and both (n=11).
Interventions	Lidocaine 1 mg/kg bolus and a 4 mg/kg iv infusion vs. morphine 0.5 mg/kg bolus + 0.02 mg/kg infusion vs. active placebo (diphenhydramine, 10 mg bolus iv + 40 mg infusion). All infusions lasted 40 min.
Outcomes	Compared with placebo, lidocaine significantly reduced stump (P < 0.01) but not phantom pain (P > 0.05) on computerized VAS. However, lidocaine was significantly better than placebo and equal to morphine in self-reported ratings of pain and satisfaction (For stump pain, the difference between means: -24.6; SE difference: 7.93; 95% CI: -8.6 to -40.6; For phantom pain, the difference between means: -22.6, SE difference: 7.33, 95% CI: -7.7 to -37.4). The NNT was 2.5 (95% CI: 1.5 to 7.4) for stump pain and 3.8 (95% CI: 1.9 to 16.6) for phantom pain. Mean plasma lidocaine level: 2.1+/-1.5 mcg/ml.
Notes	Adverse events (n/N) - nature; withdrawals: No adverse events reported. Mean sedation scores not different between placebo, morphine, and lidocaine; 1/32 withdrawn because of no pain before treatment.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Because many trials contained comparisons of different drugs, the trials in this table are listed simply in alphabetical order.
PHN: Postherpetic neuralgia; IV: intravenous; SE: standard error; n/v: nausea and vomiting; po: per os; bid: twice daily; tid: three times daily; VAS: Visual Analogue Scale; 95% CI: 95% confidence intervals; QoL = quality of life

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

Study	Reason for exclusion
Ando 2000	Acute experimental pain in healthy volunteers
Bach 1990	Double-blind, crossover study without random allocation
Català 1994	No blinding method
Dirks 2000	1. Nociceptive pain 2. Healthy volunteers
Dunlop	Drug removed from the market
Gottrup 2000	Experimental pain in healthy participants
Kastrup 1986	An extended version was published one year later
Keats 1951	1. No random allocation

Study	Reason for exclusion
	2. Acute postoperative pain
Posner 1994	No blinding method. This was a randomized, placebo control trial of intravenous lidocaine in patients with fibromyalgia.
Reljanovic 1996	No random allocation
Rowlingson 1980	Healthy participants
Sakurai 1999	1. No random allocation. 2. No blinding method.
Stracke 1992	The version published in German two years later had means and SD of pain VAS scores, necessary for the meta-analysis
Wallace 1997	Healthy participants

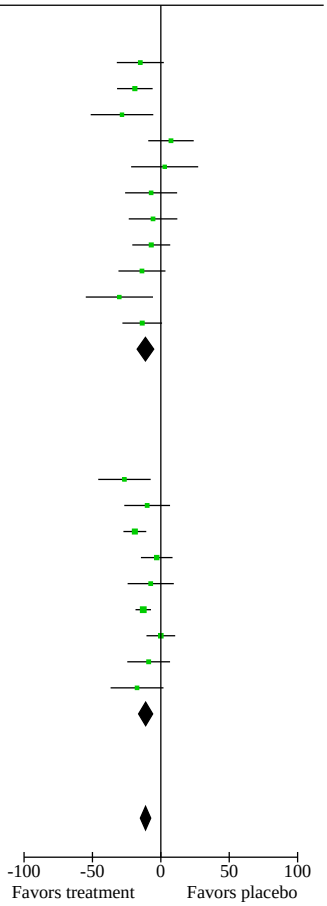
DATA AND ANALYSES

Comparison 1. Efficacy of lidocaine or mexiletine vs. placebo control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Post intervention/placebo mean VAS (0-100) pain scores (Random effects model)	20	750	Mean Difference (IV, Random, 95% CI)	-11.18 [-14.97, -7.40]
1.1.1 Lidocaine IV trials	11	373	Mean Difference (IV, Random, 95% CI)	-11.26 [-17.30, -5.22]
1.1.2 Mexiletine trials	9	377	Mean Difference (IV, Random, 95% CI)	-11.11 [-16.25, -5.97]
1.2 Significant pain relief by response rates	14	589	Odds Ratio (M-H, Random, 95% CI)	3.39 [2.08, 5.55]
1.2.1 Lidocaine	9	229	Odds Ratio (M-H, Random, 95% CI)	5.06 [2.36, 10.84]
1.2.2 Mexiletine	5	360	Odds Ratio (M-H, Random, 95% CI)	2.52 [1.47, 4.31]

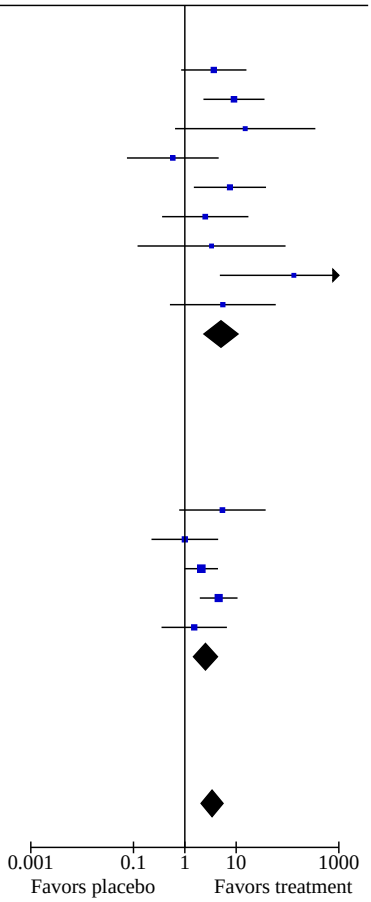
Analysis 1.1. Comparison 1: Efficacy of lidocaine or mexiletine vs. placebo control, Outcome 1: Post intervention/placebo mean VAS (0-100) pain scores (Random effects model)

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Lidocaine IV trials								
Attal 2000	31	27	16	46	22.36	16	3.9%	-15.00 [-32.18 , 2.18]
Attal 2004	19	22	22	38	22	22	6.0%	-19.00 [-32.00 , -6.00]
Backonja 2000	39	23.46	8	67.4	21.73	7	2.4%	-28.40 [-51.28 , -5.52]
Baranowski 1999	17.5	31.35	24	10.08	27.24	24	4.1%	7.42 [-9.20 , 24.04]
Bruera 1992	36.9	26	10	34.1	29.8	10	2.1%	2.80 [-21.71 , 27.31]
Kastrup 1987	33.2	26.79	15	40.3	26.34	15	3.3%	-7.10 [-26.11 , 11.91]
Marchettini 1992	59.3	25	10	65	14	10	3.7%	-5.70 [-23.46 , 12.06]
Medrik 1999	31	27.39	30	38	27.39	30	5.4%	-7.00 [-20.86 , 6.86]
Rowbotham 1991	29.8	24.5	19	43.6	29.3	19	3.9%	-13.80 [-30.97 , 3.37]
Wallace 1996	24.8	19.62	11	55.1	36.66	11	2.1%	-30.30 [-54.87 , -5.73]
Wu 2002	36.5	23.5	22	50.1	25.5	22	5.1%	-13.60 [-28.09 , 0.89]
Subtotal (95% CI)			**187**			**186**	**42.1%**	**-11.26 [-17.30 , -5.22]**
Heterogeneity: Tau² = 25.12; Chi² = 13.23, df = 10 (P = 0.21); I² = 24%								
Test for overall effect: Z = 3.65 (P = 0.0003)								
1.1.2 Mexiletine trials								
Chabal 1992	40.9	29.14	11	67.5	14.22	11	3.3%	-26.60 [-45.76 , -7.44]
Chiou-Tan 1996	77	24	11	87	15	11	4.1%	-10.00 [-26.73 , 6.73]
Dejgard 1988	27	11	16	46	13	16	10.1%	-19.00 [-27.34 , -10.66]
Fassoulaki 2002	16	19	20	19	20	24	7.0%	-3.00 [-14.55 , 8.55]
Kemper 1998	37.8	22.7	16	45.2	25.9	16	4.0%	-7.40 [-24.28 , 9.48]
Oskarsson 1997	21.85	11.05	28	34.7	11.1	31	13.8%	-12.85 [-18.51 , -7.19]
Stracke 1994	35	28	47	35	24	48	7.9%	0.00 [-10.50 , 10.50]
Wallace 2000b	28	22.1	20	36.9	28	20	4.5%	-8.90 [-24.53 , 6.73]
Wright 1997	46.5	28.3	15	63.9	26.5	16	3.2%	-17.40 [-36.73 , 1.93]
Subtotal (95% CI)			**184**			**193**	**57.9%**	**-11.11 [-16.25 , -5.97]**
Heterogeneity: Tau² = 21.75; Chi² = 13.12, df = 8 (P = 0.11); I² = 39%								
Test for overall effect: Z = 4.24 (P < 0.0001)								
Total (95% CI)			**371**			**379**	**100.0%**	**-11.18 [-14.97 , -7.40]**
Heterogeneity: Tau² = 18.59; Chi² = 26.36, df = 19 (P = 0.12); I² = 28%								
Test for overall effect: Z = 5.79 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%								



Analysis 1.2. Comparison 1: Efficacy of lidocaine or mexiletine vs. placebo control, Outcome 2: Significant pain relief by response rates

Study or Subgroup	Control Events	Control Total	Treatment Events	Treatment Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Lidocaine						
Attal 2000	11	16	6	16	8.2%	3.67 [0.85 , 15.84]
Attal 2004	16	22	5	22	9.1%	9.07 [2.31 , 35.65]
Backonja 2000	4	8	0	7	2.3%	15.00 [0.64 , 348.93]
Ellemann 1989	2	10	3	10	4.8%	0.58 [0.07 , 4.56]
Kastrup 1987	11	15	4	15	7.1%	7.56 [1.50 , 38.15]
Kvarnstrom 2003	4	12	2	12	5.3%	2.50 [0.36 , 17.32]
Kvarnstrom 2004	1	10	0	10	2.0%	3.32 [0.12 , 91.60]
Marchettini 1992	10	10	1	10	2.0%	133.00 [4.81 , 3674.23]
Sörensen 1995	4	12	1	12	3.8%	5.50 [0.51 , 59.01]
Subtotal (95% CI)		**115**		**114**	**44.6%**	**5.06 [2.36 , 10.84]**
Total events:	63		22			
Heterogeneity: Tau² = 0.28; Chi² = 10.14, df = 8 (P = 0.26); I² = 21%						
Test for overall effect: Z = 4.17 (P < 0.0001)						
1.2.2 Mexiletine						
Chabal 1992	6	11	2	11	5.3%	5.40 [0.78 , 37.50]
Kemper 1998	5	16	5	16	8.0%	1.00 [0.22 , 4.46]
Matsuoka 1996	40	110	12	56	17.9%	2.10 [0.99 , 4.42]
Matsuoka 1997	29	55	11	56	16.0%	4.56 [1.96 , 10.63]
Wright 1997	8	14	7	15	8.2%	1.52 [0.35 , 6.60]
Subtotal (95% CI)		**206**		**154**	**55.4%**	**2.52 [1.47 , 4.31]**
Total events:	88		37			
Heterogeneity: Tau² = 0.05; Chi² = 4.64, df = 4 (P = 0.33); I² = 14%						
Test for overall effect: Z = 3.38 (P = 0.0007)						
Total (95% CI)		**321**		**268**	**100.0%**	**3.39 [2.08 , 5.55]**
Total events:	151		59			
Heterogeneity: Tau² = 0.21; Chi² = 17.54, df = 13 (P = 0.18); I² = 26%						
Test for overall effect: Z = 4.88 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.14, df = 1 (P = 0.14), I² = 53.3%						



Comparison 2. Subgroup analyses for comparison 01

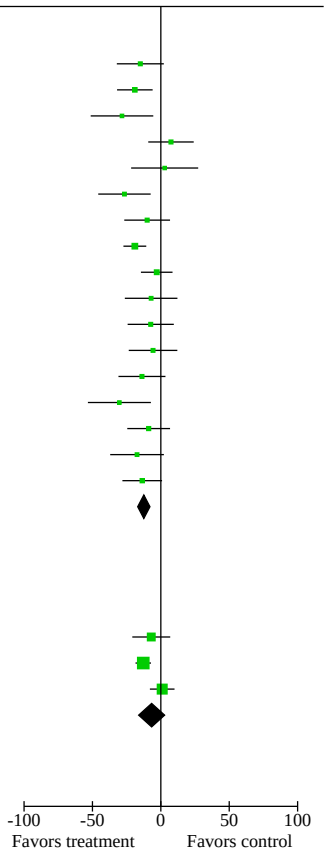
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 By sample size	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 Fewer than 25 patients	17	535	Mean Difference (IV, Random, 95% CI)	-12.44 [-16.92, -7.97]
2.1.2 More than 25 patients	3	213	Mean Difference (IV, Random, 95% CI)	-6.72 [-16.21, 2.76]
2.2 By time of outcome measurement	20	749	Mean Difference (IV, Random, 95% CI)	-10.91 [-14.91, -6.91]
2.2.1 Minutes (less than 24 h)	10	343	Mean Difference (IV, Random, 95% CI)	-11.58 [-18.34, -4.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.2 More than 24 h	10	406	Mean Difference (IV, Random, 95% CI)	-10.50 [-15.71, -5.30]
2.3 By time of outcome measurement (minus Stracke trial)	19	656	Mean Difference (IV, Random, 95% CI)	-12.21 [-15.85, -8.57]
2.3.1 Minutes (< 24 h)	10	343	Mean Difference (IV, Random, 95% CI)	-11.58 [-18.34, -4.82]
2.3.2 > 24 h	9	313	Mean Difference (IV, Random, 95% CI)	-12.85 [-16.71, -8.99]
2.4 By time of outcome measurement (minus 3 trials with wide data spread)	17	563	Mean Difference (IV, Random, 95% CI)	-13.99 [-17.25, -10.72]
2.4.1 Minutes (< 24 h)	9	295	Mean Difference (IV, Random, 95% CI)	-13.83 [-19.67, -7.99]
2.4.2 > 24 h	8	268	Mean Difference (IV, Random, 95% CI)	-14.06 [-18.00, -10.12]
2.5 By trial design	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.5.1 Crossover	15	506	Mean Difference (IV, Random, 95% CI)	-12.25 [-16.70, -7.81]
2.5.2 Parallel	5	243	Mean Difference (IV, Random, 95% CI)	-9.34 [-17.88, -0.81]
2.6 By methodological quality	20	748	Mean Difference (IV, Random, 95% CI)	-10.94 [-14.89, -6.98]
2.6.1 Score: 2-3 points	9	375	Mean Difference (IV, Random, 95% CI)	-9.31 [-15.78, -2.85]
2.6.2 Score: 4 points	7	211	Mean Difference (IV, Random, 95% CI)	-12.56 [-19.47, -5.64]
2.6.3 Score: 5 points	4	162	Mean Difference (IV, Random, 95% CI)	-12.10 [-20.00, -4.20]
2.7 By etiologic category	19		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.7.1 Peripheral (metabolic)	5	246	Mean Difference (IV, Random, 95% CI)	-11.06 [-18.97, -3.15]
2.7.2 Peripheral (infectious)	3	118	Mean Difference (IV, Random, 95% CI)	-4.45 [-16.81, 7.91]
2.7.3 Peripheral (trauma)	4	166	Mean Difference (IV, Random, 95% CI)	-8.57 [-17.23, 0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.4 Peripheral (cancer)	1	20	Mean Difference (IV, Random, 95% CI)	2.80 [-21.71, 27.31]
2.7.5 Peripheral (mixed)	3	79	Mean Difference (IV, Random, 95% CI)	-16.80 [-28.03, -5.58]
2.7.6 Central	3	98	Mean Difference (IV, Random, 95% CI)	-12.91 [-22.14, -3.67]

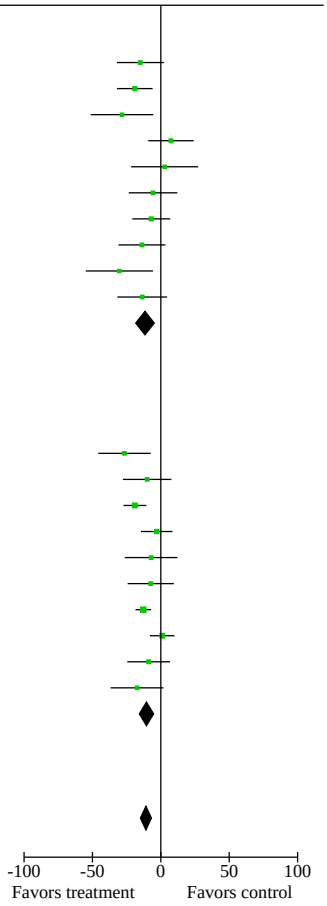
Analysis 2.1. Comparison 2: Subgroup analyses for comparison 01, Outcome 1: By sample size

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Fewer than 25 patients								
Attal 2000	31	27	16	46	22.36	16	5.4%	-15.00 [-32.18 , 2.18]
Attal 2004	19	22	22	38	22	22	8.1%	-19.00 [-32.00 , -6.00]
Backonja 2000	39	23.46	8	67.4	21.73	7	3.3%	-28.40 [-51.28 , -5.52]
Baranowski 1999	17.5	31.35	24	10.08	27.24	24	5.7%	7.42 [-9.20 , 24.04]
Bruera 1992	36.9	26	10	34.1	29.8	10	3.0%	2.80 [-21.71 , 27.31]
Chabal 1992	40.9	29.14	11	67.5	14.22	11	4.5%	-26.60 [-45.76 , -7.44]
Chiou-Tan 1996	77	24	11	87	15	11	5.6%	-10.00 [-26.73 , 6.73]
Dejgard 1988	27	11	16	46	13	16	13.6%	-19.00 [-27.34 , -10.66]
Fassoulaki 2002	16	19	20	19	20	24	9.5%	-3.00 [-14.55 , 8.55]
Kastrup 1987	33.2	26.79	15	40.3	26.94	15	4.5%	-7.10 [-26.33 , 12.13]
Kemper 1998	37.8	22.7	16	45.2	25.9	16	5.5%	-7.40 [-24.28 , 9.48]
Marchettini 1992	59.3	25	10	65	14	10	5.1%	-5.70 [-23.46 , 12.06]
Rowbotham 1991	29.8	24.5	19	43.6	29.3	19	5.4%	-13.80 [-30.97 , 3.37]
Wallace 1996	24.8	19.62	11	55.1	33.66	11	3.3%	-30.30 [-53.32 , -7.28]
Wallace 2000b	28	22.1	20	36.9	28	20	6.2%	-8.90 [-24.53 , 6.73]
Wright 1997	46.5	28.3	15	63.9	26.5	15	4.3%	-17.40 [-37.02 , 2.22]
Wu 2002	36.5	23.5	22	50.1	25.5	22	7.0%	-13.60 [-28.09 , 0.89]
Subtotal (95% CI)			**266**			**269**	**100.0%**	**-12.44 [-16.92 , -7.97]**
Heterogeneity: Tau² = 20.13; Chi² = 20.99, df = 16 (P = 0.18); I² = 24%								
Test for overall effect: Z = 5.45 (P < 0.00001)								
2.1.2 More than 25 patients								
Medrik 1999	31	27.39	30	38	27.39	30	24.0%	-7.00 [-20.86 , 6.86]
Oskarsson 1997	21.85	11.05	28	34.7	11.1	31	41.9%	-12.85 [-18.51 , -7.19]
Stracke 1994	19	25	46	18	19	48	34.1%	1.00 [-8.00 , 10.00]
Subtotal (95% CI)			**104**			**109**	**100.0%**	**-6.72 [-16.21 , 2.76]**
Heterogeneity: Tau² = 47.53; Chi² = 6.58, df = 2 (P = 0.04); I² = 70%								
Test for overall effect: Z = 1.39 (P = 0.16)								



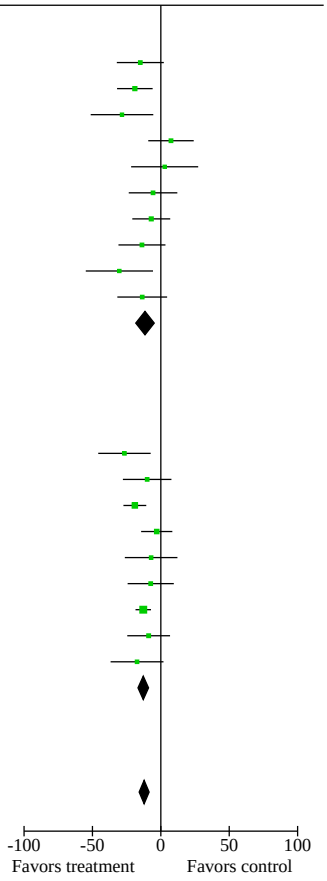
Analysis 2.2. Comparison 2: Subgroup analyses for comparison 01, Outcome 2: By time of outcome measurement

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Minutes (less than 24 h)								
Attal 2000	31	27	16	46	22.36	16	4.1%	-15.00 [-32.18 , 2.18]
Attal 2004	19	22	22	38	22	22	6.0%	-19.00 [-32.00 , -6.00]
Backonja 2000	39	23.46	8	67.4	21.73	7	2.6%	-28.40 [-51.28 , -5.52]
Baranowski 1999	17.5	31.35	24	10.08	27.24	24	4.3%	7.42 [-9.20 , 24.04]
Bruera 1992	36.9	26	10	34.1	29.8	10	2.3%	2.80 [-21.71 , 27.31]
Marchettini 1992	59.3	25	10	65	14	10	3.9%	-5.70 [-23.46 , 12.06]
Medrik 1999	31	27.39	30	38	27.39	30	5.5%	-7.00 [-20.86 , 6.86]
Rowbotham 1991	29.8	24.5	19	43.6	29.3	19	4.1%	-13.80 [-30.97 , 3.37]
Wallace 1996	24.8	19.62	11	55.1	36.66	11	2.3%	-30.30 [-54.87 , -5.73]
Wu 2002	36.5	23.5	22	50.1	36.66	22	3.7%	-13.60 [-31.80 , 4.60]
Subtotal (95% CI)			**172**			**171**	**38.8%**	**-11.58 [-18.34 , -4.82]**
Heterogeneity: Tau² = 35.83; Chi² = 13.01, df = 9 (P = 0.16); I² = 31%								
Test for overall effect: Z = 3.36 (P = 0.0008)								
2.2.2 More than 24 h								
Chabal 1992	40.9	29.14	11	67.5	14.22	11	3.5%	-26.60 [-45.76 , -7.44]
Chiou-Tan 1996	77	26	11	87	15	11	3.9%	-10.00 [-27.74 , 7.74]
Dejgard 1988	27	11	16	46	13	16	9.6%	-19.00 [-27.34 , -10.66]
Fassoulaki 2002	16	19	20	19	20	24	7.0%	-3.00 [-14.55 , 8.55]
Kastrup 1987	33.2	26.79	15	40.3	26.94	15	3.4%	-7.10 [-26.33 , 12.13]
Kemper 1998	37.8	22.7	16	45.2	25.9	16	4.2%	-7.40 [-24.28 , 9.48]
Oskarsson 1997	21.85	11.05	28	34.7	11.1	31	12.5%	-12.85 [-18.51 , -7.19]
Stracke 1994	19	25	46	18	19	48	9.0%	1.00 [-8.00 , 10.00]
Wallace 2000b	28	22.1	20	36.9	28	20	4.7%	-8.90 [-24.53 , 6.73]
Wright 1997	46.5	28.3	15	63.9	26.5	16	3.4%	-17.40 [-36.73 , 1.93]
Subtotal (95% CI)			**198**			**208**	**61.2%**	**-10.50 [-15.71 , -5.30]**
Heterogeneity: Tau² = 27.09; Chi² = 15.98, df = 9 (P = 0.07); I² = 44%								
Test for overall effect: Z = 3.95 (P < 0.0001)								
Total (95% CI)			**370**			**379**	**100.0%**	**-10.91 [-14.91 , -6.91]**
Heterogeneity: Tau² = 25.14; Chi² = 29.02, df = 19 (P = 0.07); I² = 35%								
Test for overall effect: Z = 5.34 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%								



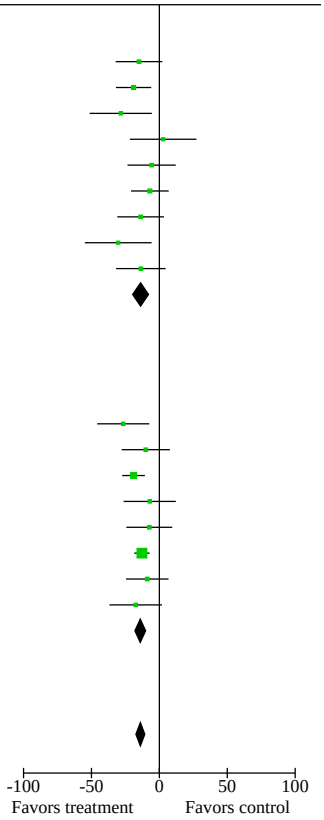
Analysis 2.3. Comparison 2: Subgroup analyses for comparison 01, Outcome 3: By time of outcome measurement (minus Stracke trial)

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 Minutes (< 24 h)								
Attal 2000	31	27	16	46	22.36	16	4.0%	-15.00 [-32.18 , 2.18]
Attal 2004	19	22	22	38	22	22	6.4%	-19.00 [-32.00 , -6.00]
Backonja 2000	39	23.46	8	67.4	21.73	7	2.4%	-28.40 [-51.28 , -5.52]
Baranowski 1999	17.5	31.35	24	10.08	27.24	24	4.2%	7.42 [-9.20 , 24.04]
Bruera 1992	36.9	26	10	34.1	29.8	10	2.1%	2.80 [-21.71 , 27.31]
Marchettini 1992	59.3	25	10	65	14	10	3.8%	-5.70 [-23.46 , 12.06]
Medrik 1999	31	27.39	30	38	27.39	30	5.8%	-7.00 [-20.86 , 6.86]
Rowbotham 1991	29.8	24.5	19	43.6	29.3	19	4.0%	-13.80 [-30.97 , 3.37]
Wallace 1996	24.8	19.62	11	55.1	36.66	11	2.1%	-30.30 [-54.87 , -5.73]
Wu 2002	36.5	23.5	22	50.1	36.66	22	3.6%	-13.60 [-31.80 , 4.60]
Subtotal (95% CI)			**172**			**171**	**38.2%**	**-11.58 [-18.34 , -4.82]**
Heterogeneity: Tau² = 35.83; Chi² = 13.01, df = 9 (P = 0.16); I² = 31%								
Test for overall effect: Z = 3.36 (P = 0.0008)								
2.3.2 > 24 h								
Chabal 1992	40.9	29.14	11	67.5	14.22	11	3.3%	-26.60 [-45.76 , -7.44]
Chiou-Tan 1996	77	26	11	87	15	11	3.8%	-10.00 [-27.74 , 7.74]
Dejgard 1988	27	11	16	46	13	16	12.4%	-19.00 [-27.34 , -10.66]
Fassoulaki 2002	16	19	21	19	20	24	7.9%	-3.00 [-14.40 , 8.40]
Kastrup 1987	33.2	26.79	15	40.3	26.94	15	3.3%	-7.10 [-26.33 , 12.13]
Kemper 1998	37.8	22.7	16	45.2	25.9	16	4.1%	-7.40 [-24.28 , 9.48]
Oskarsson 1997	21.85	11.05	28	34.7	11.1	31	19.1%	-12.85 [-18.51 , -7.19]
Wallace 2000b	28	22.1	20	36.9	28	20	4.7%	-8.90 [-24.53 , 6.73]
Wright 1997	46.5	28.3	15	63.9	26.5	16	3.2%	-17.40 [-36.73 , 1.93]
Subtotal (95% CI)			**153**			**160**	**61.8%**	**-12.85 [-16.71 , -8.99]**
Heterogeneity: Tau² = 1.11; Chi² = 8.23, df = 8 (P = 0.41); I² = 3%								
Test for overall effect: Z = 6.53 (P < 0.00001)								
Total (95% CI)			**325**			**331**	**100.0%**	**-12.21 [-15.85 , -8.57]**
Heterogeneity: Tau² = 9.69; Chi² = 21.41, df = 18 (P = 0.26); I² = 16%								
Test for overall effect: Z = 6.58 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%								



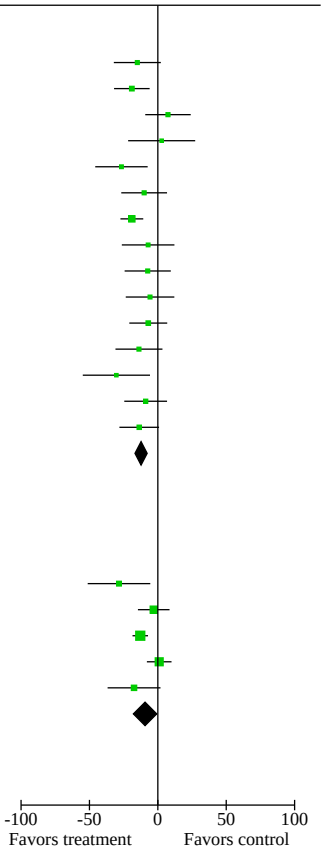
Analysis 2.4. Comparison 2: Subgroup analyses for comparison 01, Outcome 4: By time of outcome measurement (minus 3 trials with wide data spread)

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Minutes (< 24 h)								
Attal 2000	31	27	16	46	22.36	16	3.6%	-15.00 [-32.18 , 2.18]
Attal 2004	19	22	22	38	22	22	6.3%	-19.00 [-32.00 , -6.00]
Backonja 2000	39	23.46	8	67.4	21.73	7	2.0%	-28.40 [-51.28 , -5.52]
Bruera 1992	36.9	26	10	34.1	29.8	10	1.8%	2.80 [-21.71 , 27.31]
Marchettini 1992	59.3	25	10	65	14	10	3.4%	-5.70 [-23.46 , 12.06]
Medrik 1999	31	27.39	30	38	27.39	30	5.5%	-7.00 [-20.86 , 6.86]
Rowbotham 1991	29.8	24.5	19	43.6	29.3	19	3.6%	-13.80 [-30.97 , 3.37]
Wallace 1996	24.8	19.62	11	55.1	36.66	11	1.8%	-30.30 [-54.87 , -5.73]
Wu 2002	36.5	23.5	22	50.1	36.66	22	3.2%	-13.60 [-31.80 , 4.60]
Subtotal (95% CI)			**148**			**147**	**31.3%**	**-13.83 [-19.67 , -7.99]**
Heterogeneity: Tau² = 0.00; Chi² = 7.42, df = 8 (P = 0.49); I² = 0%								
Test for overall effect: Z = 4.64 (P < 0.00001)								
2.4.2 > 24 h								
Chabal 1992	40.9	29.14	11	67.5	14.22	11	2.9%	-26.60 [-45.76 , -7.44]
Chiou-Tan 1996	77	26	11	87	15	11	3.4%	-10.00 [-27.74 , 7.74]
Dejgard 1988	27	11	16	46	13	16	15.3%	-19.00 [-27.34 , -10.66]
Kastrup 1987	33.2	26.79	15	40.3	26.94	15	2.9%	-7.10 [-26.33 , 12.13]
Kemper 1998	37.8	22.7	16	45.2	25.9	16	3.7%	-7.40 [-24.28 , 9.48]
Oskarsson 1997	21.85	11.05	28	34.7	11.1	31	33.3%	-12.85 [-18.51 , -7.19]
Wallace 2000b	28	22.1	20	36.9	28	20	4.4%	-8.90 [-24.53 , 6.73]
Wright 1997	46.5	28.3	15	63.9	26.5	16	2.9%	-17.40 [-36.73 , 1.93]
Subtotal (95% CI)			**132**			**136**	**68.7%**	**-14.06 [-18.00 , -10.12]**
Heterogeneity: Tau² = 0.00; Chi² = 5.00, df = 7 (P = 0.66); I² = 0%								
Test for overall effect: Z = 7.00 (P < 0.00001)								
Total (95% CI)			**280**			**283**	**100.0%**	**-13.99 [-17.25 , -10.72]**
Heterogeneity: Tau² = 0.00; Chi² = 12.42, df = 16 (P = 0.71); I² = 0%								
Test for overall effect: Z = 8.40 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%								



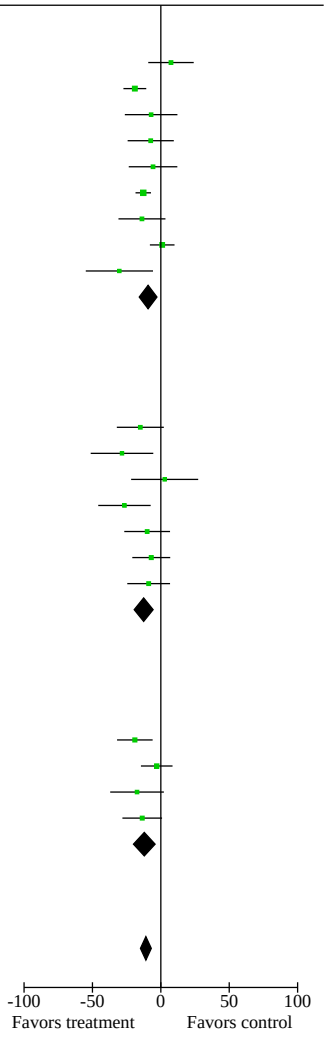
Analysis 2.5. Comparison 2: Subgroup analyses for comparison 01, Outcome 5: By trial design

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.5.1 Crossover								
Attal 2000	31	27	16	46	22.36	16	5.8%	-15.00 [-32.18 , 2.18]
Attal 2004	19	22	22	38	22	22	9.2%	-19.00 [-32.00 , -6.00]
Baranowski 1999	17.5	31.35	24	10.08	27.24	24	6.1%	7.42 [-9.20 , 24.04]
Bruera 1992	36.9	26	10	34.1	29.8	10	3.1%	2.80 [-21.71 , 27.31]
Chabal 1992	40.9	29.14	11	67.5	14.22	11	4.8%	-26.60 [-45.76 , -7.44]
Chiou-Tan 1996	77	24	11	87	15	11	6.1%	-10.00 [-26.73 , 6.73]
Dejgard 1988	27	11	16	46	13	16	17.1%	-19.00 [-27.34 , -10.66]
Kastrup 1987	33.2	26.79	15	40.3	26.94	15	4.8%	-7.10 [-26.33 , 12.13]
Kemper 1998	37.8	22.7	16	45.2	25.9	16	6.0%	-7.40 [-24.28 , 9.48]
Marchettini 1992	59.3	25	10	65	14	10	5.5%	-5.70 [-23.46 , 12.06]
Medrik 1999	31	27.39	30	38	27.39	30	8.3%	-7.00 [-20.86 , 6.86]
Rowbotham 1991	29.8	24.5	19	43.6	29.3	19	5.8%	-13.80 [-30.97 , 3.37]
Wallace 1996	24.8	19.62	11	55.1	36.66	11	3.0%	-30.30 [-54.87 , -5.73]
Wallace 2000b	28	22.1	20	36.9	28	20	6.8%	-8.90 [-24.53 , 6.73]
Wu 2002	36.5	23.5	22	50.1	25.5	22	7.7%	-13.60 [-28.09 , 0.89]
Subtotal (95% CI)			**253**			**253**	**100.0%**	**-12.25 [-16.70 , -7.81]**
Heterogeneity: Tau² = 11.91; Chi² = 16.63, df = 14 (P = 0.28); I² = 16%								
Test for overall effect: Z = 5.40 (P < 0.00001)								
2.5.2 Parallel								
Backonja 2000	39	23.46	8	67.4	21.73	7	10.0%	-28.40 [-51.28 , -5.52]
Fassoulaki 2002	16	19	20	19	20	24	21.5%	-3.00 [-14.55 , 8.55]
Oskarsson 1997	21.85	11.05	28	34.7	11.1	31	30.6%	-12.85 [-18.51 , -7.19]
Stracke 1994	19	25	46	18	19	48	25.4%	1.00 [-8.00 , 10.00]
Wright 1997	46.5	28.3	15	63.9	26.5	16	12.6%	-17.40 [-36.73 , 1.93]
Subtotal (95% CI)			**117**			**126**	**100.0%**	**-9.34 [-17.88 , -0.81]**
Heterogeneity: Tau² = 53.55; Chi² = 11.03, df = 4 (P = 0.03); I² = 64%								
Test for overall effect: Z = 2.15 (P = 0.03)								

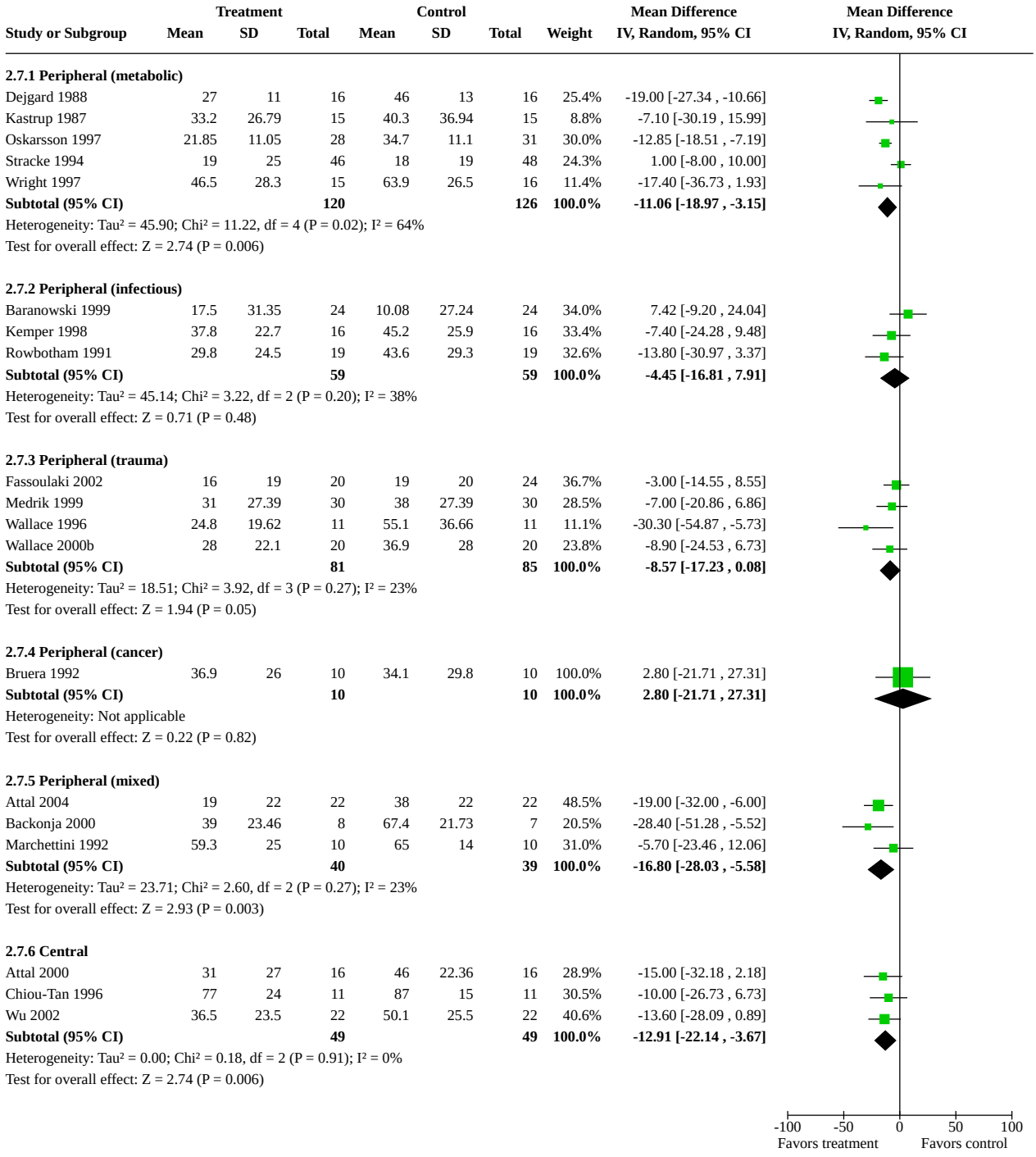


Analysis 2.6. Comparison 2: Subgroup analyses for comparison 01, Outcome 6: By methodological quality

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.6.1 Score: 2-3 points								
Baranowski 1999	17.5	31.35	24	10.08	27.24	24	4.2%	7.42 [-9.20 , 24.04]
Dejgard 1988	27	11	16	46	13	16	9.5%	-19.00 [-27.34 , -10.66]
Kastrup 1987	33.2	26.79	15	40.3	26.94	15	3.4%	-7.10 [-26.33 , 12.13]
Kemper 1998	37.8	22.7	16	45.2	25.9	16	4.1%	-7.40 [-24.28 , 9.48]
Marchettini 1992	59.3	25	10	65	14	10	3.8%	-5.70 [-23.46 , 12.06]
Oskarsson 1997	21.85	11.05	28	34.7	11.1	31	12.3%	-12.85 [-18.51 , -7.19]
Rowbotham 1991	29.8	24.5	19	43.6	29.3	19	4.0%	-13.80 [-30.97 , 3.37]
Stracke 1994	19	25	46	18	19	48	8.9%	1.00 [-8.00 , 10.00]
Wallace 1996	24.8	19.62	11	55.1	36.66	11	2.2%	-30.30 [-54.87 , -5.73]
Subtotal (95% CI)			**185**			**190**	**52.5%**	**-9.31 [-15.78 , -2.85]**
Heterogeneity: Tau² = 47.61; Chi² = 18.55, df = 8 (P = 0.02); I² = 57%								
Test for overall effect: Z = 2.82 (P = 0.005)								
2.6.2 Score: 4 points								
Attal 2000	31	27	16	46	22.36	16	4.0%	-15.00 [-32.18 , 2.18]
Backonja 2000	39	23.46	8	67.4	21.73	7	2.5%	-28.40 [-51.28 , -5.52]
Bruera 1992	36.9	26	10	34.1	29.8	10	2.2%	2.80 [-21.71 , 27.31]
Chabal 1992	40.9	29.14	11	67.5	14.22	11	3.4%	-26.60 [-45.76 , -7.44]
Chiou-Tan 1996	77	24	11	87	15	11	4.2%	-10.00 [-26.73 , 6.73]
Medrik 1999	31	27.39	30	38	27.39	30	5.4%	-7.00 [-20.86 , 6.86]
Wallace 2000b	28	22.1	20	36.9	28	20	4.6%	-8.90 [-24.53 , 6.73]
Subtotal (95% CI)			**106**			**105**	**26.4%**	**-12.56 [-19.47 , -5.64]**
Heterogeneity: Tau² = 5.61; Chi² = 6.41, df = 6 (P = 0.38); I² = 6%								
Test for overall effect: Z = 3.56 (P = 0.0004)								
2.6.3 Score: 5 points								
Attal 2004	19	22	22	38	22	22	5.9%	-19.00 [-32.00 , -6.00]
Fassoulaki 2002	16	19	20	19	20	24	6.8%	-3.00 [-14.55 , 8.55]
Wright 1997	46.5	28.3	15	63.9	26.5	15	3.3%	-17.40 [-37.02 , 2.22]
Wu 2002	36.5	23.5	22	50.1	25.5	22	5.1%	-13.60 [-28.09 , 0.89]
Subtotal (95% CI)			**79**			**83**	**21.2%**	**-12.10 [-20.00 , -4.20]**
Heterogeneity: Tau² = 13.58; Chi² = 3.78, df = 3 (P = 0.29); I² = 21%								
Test for overall effect: Z = 3.00 (P = 0.003)								
Total (95% CI)			**370**			**378**	**100.0%**	**-10.94 [-14.89 , -6.98]**
Heterogeneity: Tau² = 24.71; Chi² = 29.06, df = 19 (P = 0.07); I² = 35%								
Test for overall effect: Z = 5.42 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.52, df = 2 (P = 0.77), I² = 0%								



Analysis 2.7. Comparison 2: Subgroup analyses for comparison 01, Outcome 7: By etiologic category



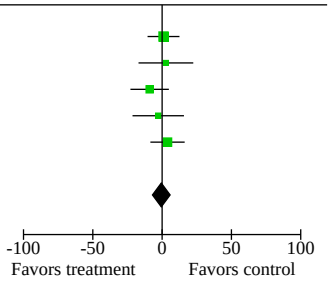
Comparison 3. Efficacy of intravenous lidocaine or its oral analogs vs. other analgesics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mean pain scores post intervention/control	5	206	Mean Difference (IV, Random, 95% CI)	-0.60 [-6.96, 5.75]

Analysis 3.1. Comparison 3: Efficacy of intravenous lidocaine or its oral analogs vs. other analgesics, Outcome 1: Mean pain scores post intervention/control

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Fassoulaki 2002	16	19	20	15	19	22	30.5%	1.00 [-10.51 , 12.51]
Lindstrom 1987	37.27	23.95	11	34.54	23.31	11	10.4%	2.73 [-17.02 , 22.48]
Medrik 1999	31	27.39	30	40	27.39	30	21.0%	-9.00 [-22.86 , 4.86]
Rowbotham 1991	29.8	24.5	19	32.6	33.2	19	11.7%	-2.80 [-21.35 , 15.75]
Wu 2002	36.5	23.5	22	32.6	18	22	26.4%	3.90 [-8.47 , 16.27]
Total (95% CI)			**102**			**104**	**100.0%**	**-0.60 [-6.96 , 5.75]**

Heterogeneity: Tau² = 0.00; Chi² = 2.16, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



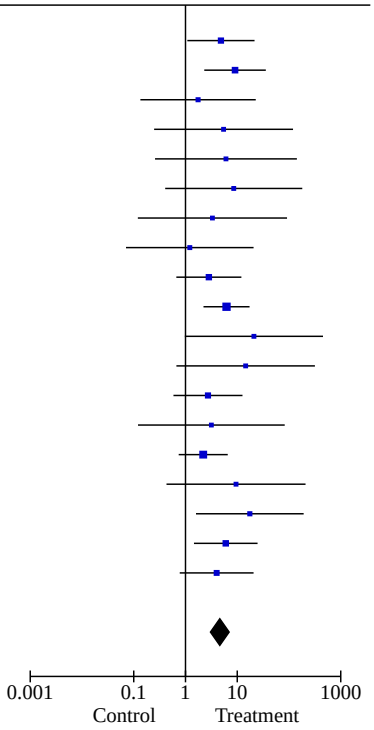
Comparison 4. Adverse effects: Lidocaine or oral analogs vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Patients with adverse effects	19	813	Odds Ratio (M-H, Random, 95% CI)	4.60 [3.04, 6.97]

Analysis 4.1. Comparison 4: Adverse effects: Lidocaine or oral analogs vs. placebo, Outcome 1: Patients with adverse effects

Study or Subgroup	Treatment Events	Treatment Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Attal 2000	11	16	5	16	7.7%	4.84 [1.09 , 21.58]
Attal 2004	16	22	5	22	9.2%	9.07 [2.31 , 35.65]
Backonja 2000	21	23	6	7	2.6%	1.75 [0.13 , 22.78]
Baranowski 1999	2	24	0	24	1.8%	5.44 [0.25 , 119.63]
Chabal 1992	2	11	0	11	1.7%	6.05 [0.26 , 142.04]
Dejgard 1988	3	16	0	16	1.9%	8.56 [0.41 , 180.52]
Ellemann 1989	1	10	0	10	1.6%	3.32 [0.12 , 91.60]
Fassoulaki 2002	1	20	1	24	2.1%	1.21 [0.07 , 20.67]
Kemper 1998	9	16	5	16	8.2%	2.83 [0.67 , 12.02]
Kieburtz 1998	22	48	6	50	16.4%	6.21 [2.23 , 17.29]
Kvarnstrom 2004	5	10	0	10	1.8%	21.00 [0.97 , 453.91]
Marchettini 1992	4	10	0	10	1.8%	14.54 [0.67 , 316.69]
Oskarsson 1997	15	95	2	31	7.3%	2.72 [0.59 , 12.62]
Rowbotham 1991	1	19	0	19	1.6%	3.16 [0.12 , 82.64]
Stracke 1994	11	46	6	48	14.5%	2.20 [0.74 , 6.55]
Sörensen 1995	3	11	0	11	1.8%	9.47 [0.43 , 208.75]
Wallace 1996	7	11	1	11	3.0%	17.50 [1.60 , 191.89]
Wallace 2000b	12	20	4	20	8.6%	6.00 [1.46 , 24.69]
Wright 1997	7	14	3	15	6.4%	4.00 [0.77 , 20.67]
Total (95% CI)		**442**		**371**	**100.0%**	**4.60 [3.04 , 6.97]**
Total events:	153		44			

Odds Ratio M-H, Random, 95% CI



Heterogeneity: Tau² = 0.00; Chi² = 8.66, df = 18 (P = 0.97); I² = 0%
Test for overall effect: Z = 7.21 (P < 0.00001)
Test for subgroup differences: Not applicable

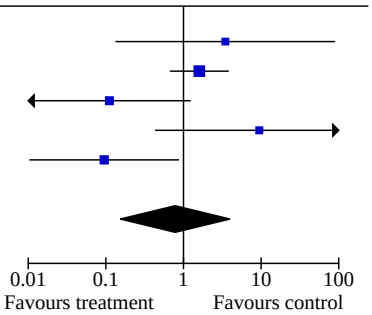
Comparison 5. Adverse effects: Lidocaine or oral analogs vs. other analgesics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Patients with adverse effects	5	205	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.15, 3.96]

Analysis 5.1. Comparison 5: Adverse effects: Lidocaine or oral analogs vs. other analgesics, Outcome 1: Patients with adverse effects

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Fassoulaki 2002	1	20	0	22	14.3%	3.46 [0.13 , 89.95]
Kieburtz 1998	22	44	15	39	30.6%	1.60 [0.67 , 3.84]
Kvarnstrom 2004	5	10	9	10	19.3%	0.11 [0.01 , 1.24]
Lindstrom 1987	3	11	0	11	15.2%	9.47 [0.43 , 208.75]
Rowbotham 1991	1	19	7	19	20.6%	0.10 [0.01 , 0.88]
Total (95% CI)		**104**		**101**	**100.0%**	**0.78 [0.15 , 3.96]**
Total events:	32		31			

Heterogeneity: Tau² = 2.05; Chi² = 11.28, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategy

#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. Mexiletine
#23. Flecainide
#24. Tocainide
#25. Oral analog*
#26. Local an*sthetic*
#27. #20 or #21 or #22 or #23 or #24 or #25 or #26
#28. #19 and #27
#29. Pain
#30. Neuro* pain
#31. #29 or #30
#32. #28 and #31

WHAT'S NEW

Date	Event	Description
29 September 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 4, 2005

Date	Event	Description
4 October 2019	Review declared as stable	See Published notes.
11 January 2019	Amended	Contact details updated.
24 July 2017	Review declared as stable	See Published notes.
12 December 2012	Amended	Contact details amended.
25 April 2012	Review declared as stable	25 April 2012 No longer updated Technique no longer used in most countries, so not seen as necessary to update. Review made stable until 2017 when we will review again the need for this title to be brought up to date. Contact the review group if you have any queries regarding this title meanwhile.
7 November 2008	Amended	Further RevMan 5 conversion changes
22 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Ivo W. Tremont-Lukats proposed this systematic review at a training workshop in systematic reviews hosted by the PaPaS Cochrane Review Group in Boston, Massachusetts, in June 2000. The protocol and search strategy were done later.
Vidya Challapalli and Ivo Tremont ran an updated search, screened studies, extracted, tabulated, and analyzed the data. Data extraction and analysis were discussed and overseen weekly, and serial drafts of the review were edited by Daniel Carr. Joseph Lau reviewed and edited all statistical analyses.
Ewan McNicol performed a significant portion of the editing and final rewriting, contributed to the data extraction, and coordinated the assembly of various portions of text and data into the appropriate format. All reviewers contributed to the drafts, edition, and final published version.

DECLARATIONS OF INTEREST

None known

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Internal sources

- Financial Support: The Richard Saltonsall Charitable Foundation and the Evenor Armington Fund, USA

External sources

- No sources of support supplied

NOTES

2017

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

2019

We performed another restricted search in September 2019 but did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors, and we will reassess the review for updating in 2020. If appropriate, we will update the review sooner if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

2020

We performed another restricted search in September 2020 but again did not identify any potentially relevant studies likely to change the conclusions. This area of research is not active and therefore this review has now been stabilised following discussion with the authors and editors; we will reassess the review for updating in 2025. If appropriate, we will update the review sooner if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anesthetics, Intravenous [administration & dosage]; Anesthetics, Local [*administration & dosage]; Flecainide [administration & dosage]; Lidocaine [*administration & dosage] [analogs & derivatives]; Mexiletine [administration & dosage]; Nervous System Diseases [*complications]; Pain [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Tocainide [administration & dosage]

MeSH check words

Humans