Systemic Administration of Local Anesthetics to Relieve Neuropathic Pain: A Systematic Review and Meta-Analysis

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We reviewed randomized controlled trials to determine the efficacy and safety of systemically administered local anesthetics compared with placebo or active drugs. Of 41 retrieved studies, 27 trials of diverse quality were included in the systematic review. Ten lidocaine and nine mexiletine trials had data suitable for meta-analysis ($n = 706$ patients total). Lidocaine (most commonly 5 mg/kg IV over 30–60 min) and mexiletine (median dose, 600 mg daily) were superior to placebo (weighted mean difference on a 0–100 mm pain intensity visual analog scale = −10.60; 95% confidence interval: −14.52 to −6.68; $P < 0.00001$) and equal to morphine, gabapentin, amitriptyline, and amantadine (weighted mean difference = −0.60; 95% confidence interval: −6.96 to 5.75) for neuropathic pain. The therapeutic benefit was more consistent for peripheral pain (trauma, diabetes) and central pain. The most common adverse effects of lidocaine and mexiletine were drowsiness, fatigue, nausea, and dizziness. The adverse event rate for systemically administered local anesthetics was more than for placebo but equivalent to morphine, amitriptyline, or gabapentin (odds ratio: 1.23; 95% confidence interval: 0.22 to 6.90). Lidocaine and mexiletine produced no major adverse events in controlled clinical trials, were superior to placebo to relieve neuropathic pain, and were as effective as other analgesics used for this condition.

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Lidocaine is a local anesthetic of the amide type also used systemically as an antiarrhythmic drug. Early reports described the use of IV lidocaine or procaine to relieve cancer and postoperative pain (1–4). Subsequent experimental studies indicated that lidocaine produces analgesia by blockade of peripheral and central sodium ion gate channels, including in the spinal dorsal horn (5), and if given IV can alleviate deafferentation pain or central pain (6). More recent research has suggested that the antinociceptive action of lidocaine is more complex and that inhibition of neuronal ectopic discharges is only one of several mechanisms involved (7). Mao and Chen (8) suggest that lidocaine administration for neuropathic pain has regained much attention over the past decade for two reasons: first, animal and laboratory data have provided a plausible mechanism by which lidocaine might be clinically effective for neuropathic pain; and second, oral analogues of local anesthetics have been developed to permit chronic maintenance therapy. The International Association for the Study of Pain defines neuropathic pain as "pain resulting from damage to the peripheral or central nervous system" (9). Neuropathic pain has several key clinical characteristics: variable onset after injury, lancinating and spontaneous character, association with allodynia and hyperesthesia, and evoked summation and hyperpathia (10).

Neuropathic pain may be attributable to primary afferent nociceptive or non-nociceptive input or to spontaneous ectopic discharges without activation of peripheral nociceptors (8,11). Cell membranes of injured peripheral nerves express sodium channels with unusual density and produce persistent spontaneous discharges that maintain a central hyperexcitable state (12). Ectopic discharges can be initiated along the injured nerve, in the dorsal root ganglion, and in peripheral neuromata (13–17). Lidocaine inhibits these aberrant electrical discharges at concentrations well below those necessary to produce conduction blockade in nerves. Studies in animal preparations clearly indicate that systemically administered lidocaine can silence

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ectopic discharges without blocking nerve conduction (11,14,16,18,19). Further studies have shown that the systemic administration of local anesthetics provides clinical analgesia in a broad range of neuropathic pain states (8,11,20–25).

Clinical trials testing lidocaine or its oral analogues for neuropathic pain have, in general, enrolled few patients, used varied dosage regimens, had different experimental designs, and assessed end-points across diverse time periods in patients with neuropathic pain of different etiologies. The result is a lack of clear definition on the role of these drugs in the treatment of neuropathic pain. To consolidate this sometimes contradictory literature, we have critically evaluated and quantitatively synthesized the existing data on the effect of local anesthetics administered systemically to relieve neuropathic pain.

Methods

Our objectives were 1) To determine if systemically administered local anesthetics relieve neuropathic pain and to quantify the degree of pain relief compared with other control interventions (placebo and active control drugs); 2) To examine whether particular clinical subpopulations benefit more from this therapy; and 3) To assess the safety of these agents.

We performed a sensitive search (26) to identify published trials with parallel or crossover design in patients with neuropathic pain of any etiology. We combined a series of search terms relevant to randomized double-blind, placebo-controlled trials with pain-specific terms and with the subject headings "lidocaine," "lignocaine," "mexiletine," "flecainide," and "tocainide." The search strategy was adapted to each of the following databases: The Cochrane Central Register of Controlled Trials (Software Update, version 4, 2000); EMBASE (January 1980 to December 2002); MEDLINE (January 1966 to December 2002); CancerLit (1963 to October 2002); LILACS; and the System for Information on Grey Literature in Europe (SIGLE). This latter database was used to search for conference proceedings. We placed no language restriction on the search. We also reviewed the reference sections of retrieved articles to identify additional randomized controlled trials. We contacted investigators in this field for assistance in identifying other published or unpublished trials or to request additional data on published trials.

Three reviewers independently screened all titles and abstracts identified in the literature search. The titles and abstracts were not blinded as to author names, affiliated institutions, journal of publication, or study results. Identified trials were then examined for internal validity using the Oxford Quality Score criteria as described by Jadad et al. (27) and examined for other methodological bias. The reviewers resolved any disagreement by discussion.

We extracted data on patient characteristics, study design methods, interventions, outcome measurements, and adverse events from the original papers. The outcomes and instruments to measure them varied across studies. Outcome measurements were categorized as binary or continuous. For continuous data, a change in the 0–100 mm Visual Analog Scale (VAS) ratings of pain intensity was the most common pain-related outcome (28–54). When possible, we linearly transformed other scales or categorical assessments so as to map into this scale. Continuous data included medians, means with standard deviations, or SEM. Because medians do not measure variance we did not analyze medians. If no SD was presented, we calculated it from SEM and sample size. Adverse events were recorded as presented and defined by original authors; no distinction was made as to their severity or to whether they were major or minor, and no judgment was made regarding drug causation. We combined the aggregate, continuous data on pain response and dichotomous data on adverse events to obtain a pooled effect size for each outcome.

We analyzed the data collected with MetaView (version 4.1), the companion module for RevMan 4.1.1 (both available at www.cochrane.org). We calculated the weighted mean differences (WMD) between placebo control or active control and treatment groups. Every analysis was assessed for statistical heterogeneity using the χ^2 and I^2 tests. All data were combined with a random effects model which incorporates both between-studies and within-study heterogeneity. We calculated the odds ratio (OR) for adverse events.

Results

Our literature search identified 1902 potentially relevant titles. Forty-one trials of systemically administered local anesthetic-type drugs met inclusion criteria. Fourteen trials were excluded: two were duplicate publications (55,56); one study of flecainide was terminated when the drug was removed from the market (57); five trials examined the use of IV lidocaine in experimentally induced acute pain in normal volunteers (58–62); three trials did not have or describe random allocation (63–65); two trials were unblinded (66,67); and one study was single blinded, without random allocation (1). Twenty-seven randomized, double-blind, controlled clinical trials for chronic neuropathic pain were included (28–54): 13 used lidocaine; 12 used mexiletine; one tested lidocaine and mexiletine sequentially (37); and one used tocainide (41). Eight studies were parallel trials. Nineteen had a crossover design. Two of the 19 trials did not specify washout periods (41,42). Three randomized studies

appeared as abstracts (29,43,44). We retrieved complete information from one of these trials by contacting the author (29). The age (mean ± SD) of the participants in all included trials was 51.7 ± 10.3 yr. We expected that trials enrolling participants with different diseases despite having overlapping etiological features (e.g., poststroke and spinal cord injury pain, or causalgia/reflex sympathetic dystrophy and diabetic polyneuropathy) would contribute to heterogeneity (Table 1).

Eleven clinical trials (41%) were of good methodological quality, scoring four points (28,29,31–33,45,52) or five points (36,40,53,54) on the Jadad scale (27). Sixteen trials (59%) scored two points (38,43,44) or three points (30,34,35,37,39,41,42,46–51). The median score was three for all trials with either lidocaine or its oral analogues. Of the 27 trials included in this review, seven (26%) described a method for random allocation (29,31,32,36,40,53,54); six (22%) included sample size calculations (33,36,40,45,53,54), and 10 (37%) described some method to check that blinding was effective (28,29,31,35,36,40,45,46,52,54). The sample sizes of the arms receiving lidocaine or oral analogues varied but in general were small; the median size for all trials was 28 (range, 8–87).

Data Comparisons

Meta-Analysis of Relief of Spontaneous Pain with IV Lidocaine or Oral Mexiletine Versus Placebo. All placebo-controlled trials involving lidocaine and mexiletine that provided continuous data (means and SD or SEM) on pain relief were eligible for meta-analysis (Fig. 1). For trials using more than one dose of lidocaine or mexiletine, the largest dose was selected. For trials measuring pain at different times, the last measurement time was most commonly chosen. From the trial reported by Bruera et al. (31) we pooled the data from all time points because of the unusually large number of measurements; however, the negative findings of this study would not have been affected were we to have used data from any single time point. We pooled daytime and nocturnal pain scores reported in one trial (46), and for a trial on postamputation pain evaluating stump and phantom pain, we chose stump pain (54).

Pretreatment and posttreatment mean pain scores were available from 10 lidocaine and 9 mexiletine trials ($n = 706$), for a total of 349 patients receiving the treatment drug and 357 patients receiving placebo. The summary effect size for lidocaine and mexiletine pooled together indicates that both drugs were superior to placebo in relieving chronic neuropathic pain (WMD = −10.60 mm; 95% CI: −14.52 to −6.68 mm; $P < 0.00001$). Both drugs had similar efficacy in decreasing VAS pain scores: in the lidocaine trials included for meta-analysis 165 patients received lidocaine and 164 patients were treated with placebo. Lidocaine was superior to placebo (WMD = −10.02 mm; 95% CI: −16.51 to −3.54 mm, $P = 0.002$); in the mexiletine trials, 184 patients received mexiletine and 193 patients received placebo. Two trials had a wide dispersion of data around the mean (36,48). The combined effect size also favored mexiletine over placebo (WMD = −10.97 mm; 95% CI: −16.14 to −5.80 mm, $P = 0.0001$).

Meta-Analysis of Either Lidocaine or Mexiletine Versus Other Active Treatments. Five trials ($n = 206$: 102 treated with lidocaine or analogues, 104 treated with an active control) compared the analgesia obtained with local anesthetic-type drugs with that obtained with other active controls: carbamazepine (41), gabapentin (36), amantadine (45), and morphine (47,54) (Fig. 2). There was no evidence of heterogeneity ($\chi^2 = 2.16$; $df = 4$; $P = 0.71$) and no evidence that these drugs were better than lidocaine or oral congeners to relieve neuropathic pain (WMD = −0.60 mm; 95% CI: −6.96 to 5.75 mm).

Subgroup Analyses

Sample Size. Trials were categorized into 2 subgroups: fewer than 25 participants ($n = 16$, 6 mexiletine trials and 10 lidocaine trials); and more than 25 participants ($n = 3$, 2 mexiletine trials and one lidocaine trial). Despite the larger number of trials and the fact that nearly 40% were studies with mexiletine, the subgroup of studies with fewer than 25 patients was not statistically heterogeneous, the less numerous subgroup of studies that enrolled more than 25 patients was statistically heterogeneous.

Time of Outcome Measurement. Stratification analysis indicated that the time of outcome assessment may contribute to the heterogeneity of the study findings. Although there was no indication of statistical heterogeneity in the subgroup with outcome measurements recorded up to 24 h ($n = 9$, all lidocaine trials), the second subgroup (outcome measurements recorded later than 24 h, $n = 10$, including 2 lidocaine trials) was borderline heterogeneous ($P = 0.07$). Further, exclusion of one trial (48) lessened the heterogeneity considerably. In fact, when all trials were combined to yield a global effect size, the statistical heterogeneity was borderline ($\chi^2 = 27.1$; $df = 18$; $P = 0.08$). We performed an analysis in which all trials with widely spread data were suppressed (30,36,48). Effect sizes for both subgroups separately or combined into one summary statistic showed no evidence of statistical heterogeneity ($\chi^2 = 11.40$; $df = 15$; $P = 0.72$).

Trial Design. Trials were classified according to design as either crossover or parallel trials. χ^2 tests for heterogeneity suggested that the crossover trials were

Table 1. Randomized Double-Blind Controlled Trials Included in the Present Review

Study	Methods	Controls	Number of participants; type of pain	Interventions	Author-reported outcomes and conclusion	Adverse events (n/N)-nature; withdrawals	Jadad quality scale
Attal, 2000 (28)	Crossover, with 3-wk washout	Placebo −0.9% saline	18 (16 evaluable); neuropathic pain from stroke and spinal cord injury	Lidocaine: 5 mg/kg × 30 min	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 postinjection. During 3-week follow-up, no difference in pain between lidocaine 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 versus 6/32 with placebo	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	4
Backonja, 2000 (29)	Parallel pilot	Placebo −0.9% saline	32 (31 evaluable); peripheral neuropathic pain	Lidocaine at 1, 3, and 5 mg/kg/h IV infusions over 6 h, plus an observation time of 4 h (Total: 10 h)	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	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.	4
Baranowski, 1999 (30)	Crossover, with 1-wk washout	Placebo −0.9% saline	24; PHN	Lidocaine IV 2-h infusion at 1 and 5 mg/kg	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	Lidocaine (5 mg/kg): 2/24—circumoral paresthesia	3
Bruera, 1992 (31)	Crossover, with 48-h washout	Placebo −0.9% saline	10; neuropathic pain from cancer	Lidocaine 5 mg/kg IV	Lidocaine no better than placebo. Pain levels not significantly lower than pretreatment scores	No adverse events noted	4
Chabal, 1992 (32)	Crossover, with 1-wk washout	Placebo capsule	14 (11 evaluable); peripheral neuropathic pain (idiopathic painful polyneuropathy $n = 3$; other peripheral or cranial nerve injuries, $n = 8$)	Mexiletine starting at 150 mg po bid × 3 days, with titration up to 750 mg po/day × 15 days. Once at steady-level, patients were followed on that dose × 4 wk, tapered in 1 wk, and switched to alternate treatment	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	Mexiletine: 2/11—mild nausea. No withdrawals.	4
Chiou-Tan, 1996 (33)	Crossover, with 1-wk washout	Placebo capsule	15 (11 evaluable); dysesthetic pain from spinal cord injuries	Mexiletine 450 mg po daily	No difference between mexiletine and placebo	Adverse events not reported; Withdrawals (4/15): atrial fibrillation ($n = 1$); imprisonment ($n = 1$); noncompliance ($n = 2$).	4
Dejgard, 1988 (34)	Crossover, with 4-wk washout	Placebo capsule	16; diabetic neuropathy >6 months duration	Mexiletine 10 mg/kg/day after titration from 150 mg/day	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	Mexiletine: 3/16	3
Ellemann, 1989 (35)	Crossover, with 1-wk washout	Placebo −0.9% saline	20; neuropathic cancer pain ($n = 10$) polyneuropathy ($n = 7$) plexopathy ($n = 3$)	Lidocaine 5 mg/kg IV	No difference between placebo or lidocaine to reduce allodynia ($P = 0.99$)	Lidocaine: 1/10—transient drowsiness	3
Fassoulaki, 2002 (36)	Parallel	Placebo capsule; Active-gabapentin	75 (67 evaluable); breast cancer undergoing mastectomy or lumpectomy with axillary node dissection	Mexiletine 600 mg po/day, gabapentin 1200 mg po/day, or placebo divided in three equal doses, × 10 days	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 with those who took mexiletine (1/20), or gabapentin (1/22) ($P = 0.033$, Fisher's exact test)	Mexiletine: 1/21-n/v Gabapentin: 0/22; Placebo: 0/24	5
Galer, 1996 (37)	Crossover, with 1-wk washout	No control—see "Interventions"	Nine; diabetic polyneuropathy ($n = 5$), other polyneuropathy ($n = 1$), nerve injury ($n = 2$), and lumbosacral arachnoiditis ($n = 1$)	Lidocaine 2 mg/kg, 5 mg/kg IV, × 45 min in separate sessions. After second treatment, mexiletine 300 mg/day with possibility to titrate to 1200 mg/day	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.	Lidocaine: 1/9—weakness after each infusion	3
Kastrup, 1987 (38)	Crossover, with 5-wk washout	Placebo −0.9% saline	15; painful diabetic neuropathy	Lidocaine 5 mg/kg IV infusion × 30 min	Patients on lidocaine had significantly less pain that 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	No adverse events reported with placebo or lidocaine	2
Kemper, 1998 (39)	Crossover, with 1-wk washout	Placebo capsule	22 (16 evaluable); HIV-1-related painful polyneuropathy	Mexiletine up to 600 mg/day × 6 wk	No difference between placebo and mexiletine ($P = 0.76$). 31% of patients had less pain compared with 31% of patients when they received placebo. Six patients (38%) did not feel relief with either drug	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—ECG changes	3

Table 1. (Continued)

Study	Methods	Controls	Number of participants; type of pain	Interventions	Author-reported outcomes and conclusion	Adverse events (n/N)-nature; withdrawals	Jadad quality scale
Kieburtz, 1998 (40)	Parallel	Placebo capsule; Active-amitriptyline	145 (126 evaluable); HIV-1-related painful polyneuropathy	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	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 μg/mL	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).	5
Lindstrom, 1987 (41)	Crossover, washout unclear	Active-carbamazepine	12 (8 evaluable); idiopathic trigeminal neuralgia	Tocainide 20 mg/kg/tid × 2 wk or carbamazepine × 2 wk (dose not stated)	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)	Tocainide: 3/11-nausea (n = 1), paresthesias (n = 1), and skin rash that prompted discontinuation of the drug (n = 1); One patient had no pain scores to compare.	3
Marchettini, 1992 (42)	Crossover, washout not reported	Placebo −0.9% saline	10; peripheral neuropathic pain. In 7 patients pain was related to surgery.	Lidocaine 1.5 mg/kg over 1 min	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 difference between placebo and lidocaine. Mild pain reduction w/ placebo in 1/10 patients. Disappearance of allodynia in 6/6 patients.	Lidocaine: 4/10–light-headedness; No withdrawals.	3
Matsuoka, 1996 (43)	Parallel	Placebo capsule	169; diabetic polyneuropathy	Mexiletine 100 mg po tid, mexiletine 150 mg po tid	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 and Coukell (86). 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%)	No mention of adverse events	2
Matsuoka, 1997 (44)	Parallel	Placebo capsule	118 (111 evaluable); diabetic polyneuropathy	Mexiletine 100 mg po tid × 2 wk	Mexiletine was better than placebo at the end of 1st wk (42% versus 17.4%, P < 0.05) and at the 2nd wk (53% versus 20%, P < 0.05)	No mention of adverse events, toxicity, or withdrawals.	2
Medrik and Goldberg, 1999 (45)	Crossover, with 2 to 7-day washout	Placebo −0.9% saline; Active-amantadine	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	Lidocaine 5 mg/kg or amantadine 2.5 mg/kg IV × 2h	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 evolved pain (P < 0.05).	24/30 patients reported adverse events: 37 total events with lidocaine and 3 with placebo.	4
Oskarsson, 1997 (46)	Parallel	Placebo capsule	126 (115 evaluable); painful diabetic neuropathy	Mexiletine 225 mg, (group 1); 450 mg (group 2); 675 mg (group 3) po tid.	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.	Mexiletine: 15/84; Placebo: 2/31	3
Rowbotham, 1991 (47)	Crossover, with 48-h washout	Placebo −0.9% saline Active-morphine	19; PHN for >3 months	Lidocaine: target dose = 5 mg/kg IV versus IV morphine	Both lidocaine and morphine were significantly better than placebo (P = 0.04 and P = 0.02, respectively). Lidocaine not different than morphine.	Withdrawals: 1/19 on lidocaine	3
Stracke, 1994 (48)	Parallel	Placebo capsule	95; diabetic neuropathy	Mexiletine 450–675 mg po daily	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	Mexiletine: 11/46 (only with 675 mg/day); Placebo: 6/48	3
Sorensen, 1995 (49)	Crossover, with 1-wk washout	Placebo −0.9% saline	12; fibromyalgia	Lidocaine 5 mg/kg IV × 30 min	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).	Lidocaine: 3/12–nausea and perioral numbness (n = 2), drowsiness, dysarthria, and tremor (n = 1)	3
Wallace, 1996 (50)	Crossover, with 1-wk washout	Placebo −0.9% saline	11; neuropathic pain from peripheral nerve injury	Lidocaine IV infusions targeted to deliver plasma concentrations of 0.5, 1.0, 1.5, 2.0 and 2.5 μg/mL	Lidocaine caused a statistically significant reduction in pain scores compared with placebo (P < 0.05) at concentrations >= 1.5 μg/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)	Lidocaine: 7/11—lightheadedness (n = 6), nausea (n = 1), Placebo: 1/11— lightheaded-ness	3
Wallace, 2000 (51)	Crossover, with 1-wk washout	Placebo–diphenhydra-mine IV	16; complex regional pain syndrome types I and II	Lidocaine IV infusions targeted to deliver plasma concentrations of 1.0, 1.5, 2.0 and 3.0 μg/ml or diphenhydramine 70–80 mg	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	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	3

Table 1. (Continued)

Study	Methods	Controls	Number of participants; type of pain	Interventions	Author-reported outcomes and conclusion	Adverse events (n/N)-nature; withdrawals	Jadad quality scale
Wallace, 2000 (52)	Crossover, with 1-wk washout	Placebo capsule	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).	Mexiletine starting at 150 mg po bid titrated up to 300 mg po tid over 10 days	18/20 patients tolerated mexiletine 900 mg/day. Peak plasma mexiletine levels were 0.54 μg/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	Mexiletine: 12/20—non-GI (trismus, headache, agitation, nightmares, and tremors) (n = 11), nausea and sedation (no rates given). Placebo: 4/20	4
Wright, 1997 (53)	Parallel	Placebo capsule	31 (29 evaluable); peripheral diabetic neuropathy	Mexiletine titrated over 4 days to 200 mg po tid	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.	Lidocaine: 7/15; Placebo: 3/14; Withdrawals: 6/31 (4 from adverse events, 2 from placebo, and 2 from mexiletine).	5
Wu, 2002 (54)	Crossover, with 24-h washout	Placebo—diphenhydramine IV Active-morphine IV	32 (31 evaluable); postamputation pain: stump pain alone (n = 11) phantom pain alone (n = 9), and both (n = 11).	Lidocaine 1 mg/kg bolus and a 4 mg/kg IV infusion versus morphine 0.5 mg/kg bolus + 0.02 mg/kg infusion versus active placebo (diphenhydramine, 10 mg bolus IV + 40 mg infusion). All infusions lasted 40 min.	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 μg/mL.	No adverse events reported. Mean sedation scores not different between placebo, morphine, and lidocaine; 1/32 withdrawn because of no pain before treatment.	5

Because many trials contained comparisons of different drugs, the trials in this table are listed simply in alphabetical order.

95% CI = 95% confidence intervals; bid = twice daily; CRPS = complex regional pain syndrome; CSQ = coping strategies questionnaire; ECG = electrocardiogram; FIS = four-item symptom score; GI = gastrointestinal; HIV = human immunodeficiency virus; IV = intravenous; NNT = number needed to treat; n/v = nausea and vomiting; PHN = postherpetic neuralgia; po = per os; QoL = quality of life; SE = standard error; tid = three times daily; VAS = visual analog scale; WHYS = West Haven-Yale Multidimensional Pain Inventory.

less heterogenous than the parallel trials (P = 0.29 and P = 0.02, respectively), largely because of three of the trials within the latter group (36,40,48). However, statistical tests such as χ^2 are insensitive measures of heterogeneity (68), and, in fact, visual inspection of the forest plots for both types of trials disclosed heterogeneity in both. Therefore, trial design may be a source of heterogeneity.

Methodological Quality. We used the Jadad score (27) to categorize trials into 3 subgroups: between 2 to 3 points (low and fair quality, n = 8); 4 points (good quality, n = 8); and studies with 5 points (very good quality, n = 3). The reported estimates of efficacy did not differ significantly according to study quality.

Etiology. All trials were stratified into six subgroups by etiology:

1) Peripheral, metabolic: five trials, of which four used mexiletine and one used lidocaine. The only disease was diabetic polyneuropathy.

2) Peripheral, infectious: three trials including human immunodeficiency virus (HIV)-1-related polyneuropathy treated with mexiletine (n = 1) and postherpetic neuralgia treated with lidocaine (n = 2).

3) Peripheral, posttraumatic: four trials with mexiletine and lidocaine (two each).

4) Peripheral, cancer: one trial using lidocaine.

5) Peripheral, mixed: two trials using lidocaine.

6) Central/mixed, vascular or posttraumatic: three trials included participants with pain resulting from postamputation, stroke, and spinal cord injury. Lidocaine was used in two of these trials, while mexiletine was used in one.

The subgroup with peripheral neuropathic pain of metabolic etiology showed heterogeneity. No conclusion can be drawn from subgroup 4 (peripheral, cancer), as there is only one trial published with data that could be included in the meta-analysis. These findings suggest that etiology is another important source of clinical and statistical heterogeneity.

Adverse Events

The most common adverse events noted in the retrieved trials were nausea, vomiting, abdominal pain, diarrhea, dizziness, and perioral numbness. Less frequent side effects were metallic taste, tremor, dry mouth, insomnia, allergic reactions, and tachycardia. Serious adverse events, such as cardiac arrhythmias and hemodynamic instability, were notably absent from these trials. With mexiletine the most common adverse events were nausea and vomiting (17.24%), slightly more than the proportion of patients receiving lidocaine who presented with these symptoms (16.4%). Side effects referable to the central nervous system were more frequent in those patients who received lidocaine, with dizziness ranking first (29.5%). Instead, neurologic symptoms in the patients treated with mexiletine were far less frequent: for example, dizziness was reported in two patients (39,46), and tremor in two other patients (32,46).

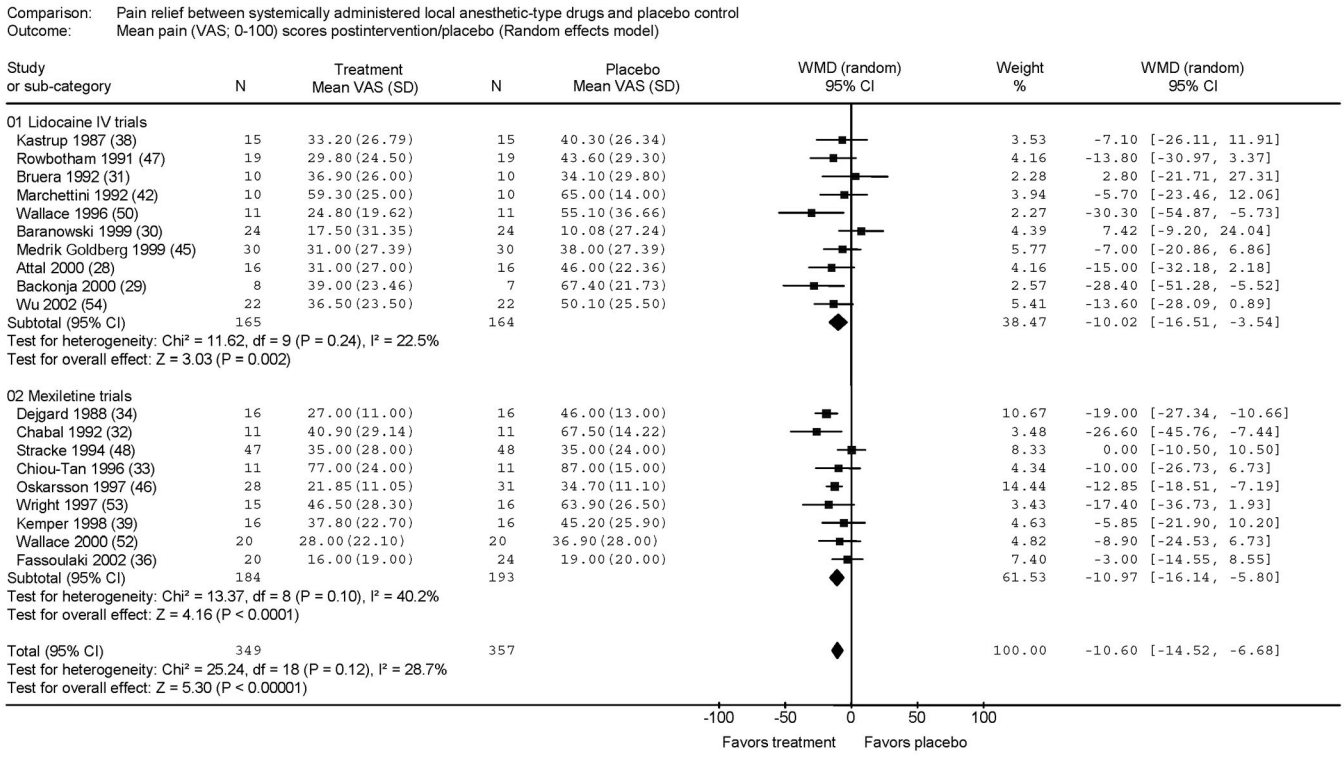

Figure 1. Comparison of pain relief between systemically administered local anesthetic-type drugs and placebo control. Meta View software is uncensored and converts numbers in outcomes to two decimal places regardless of initial value input. VAS = visual analog scale; WMD = weighted mean difference; CI = confidence interval.

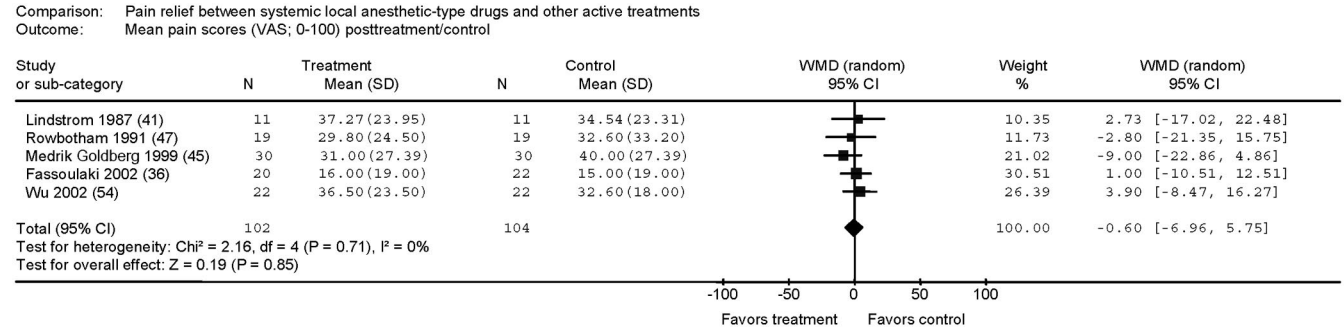

Figure 2. Comparison of pain relief between systemically administered local anesthetic-type drugs and other active treatments. Active control drugs: carbamazepine (41), morphine (47,54), amantadine (45), and gabapentin (36). Meta View software is uncensored and converts numbers in outcomes to two decimal places regardless of initial value input. VAS = visual analog scale; WMD = weighted mean difference; CI = confidence interval.

Lidocaine and Oral Analogues Versus Placebo. Twenty studies provided rates of adverse events for placebo and lidocaine or oral analogues (28–36,38–40,42,46–50,52,53) (Fig. 3). Three of these (31,33,38) do not appear in Figure 3 because they found no adverse events in participants exposed to the treatment drug or placebo. Of 749 participants, 410 were treated with lidocaine or mexiletine and 339 received placebo. One-hundred-thirty-two patients (32.2%) receiving the test drug experienced adverse events, compared with 39 patients (11.5%) given placebo (OR = 4.16, 95% CI: 2.68 to 6.46). There was no evidence of statistical heterogeneity ($P = 0.98$). These results indicate that treatment with lidocaine or mexiletine was associated with significantly more adverse events than placebo.

Lidocaine and Oral Analogues Versus Other Analgesics Used as Active Controls. Because of possible safety issues related to using local anesthetics systemically for indications other than cardiac arrhythmias, we compared lidocaine and oral analogues with other active control drugs, with the aim of determining their relative safety in the treatment of neuropathic pain. Of

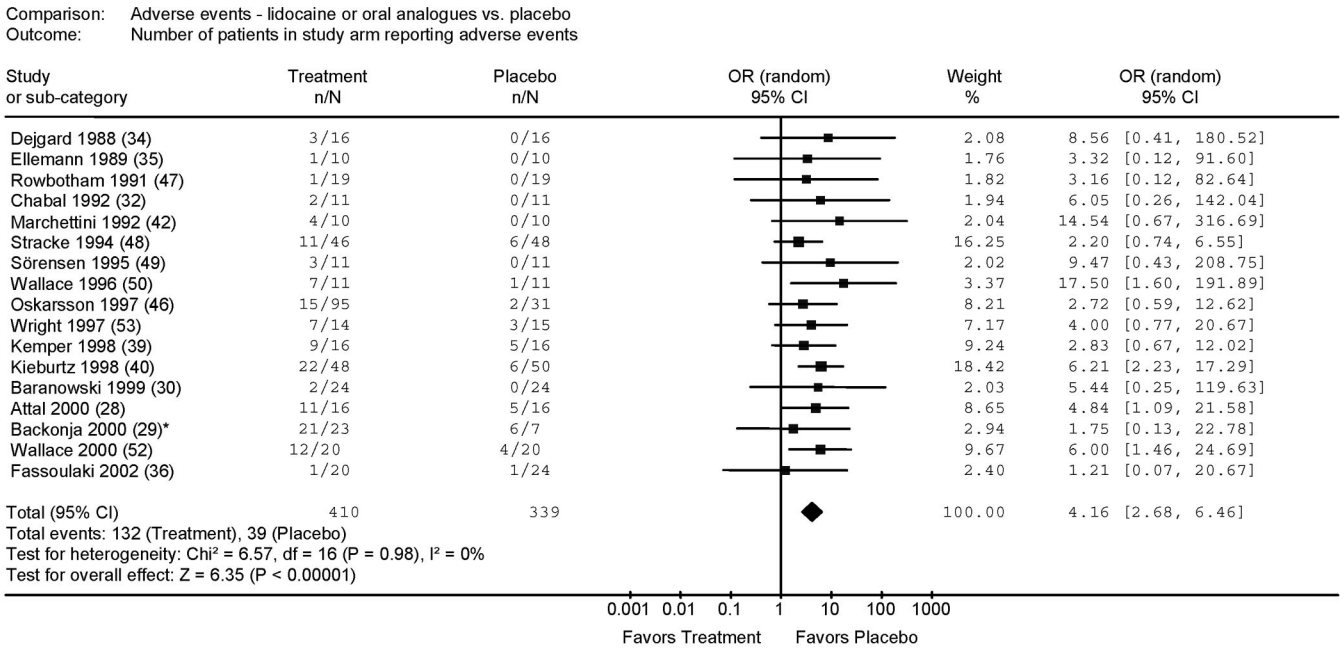

Figure 3. Comparison of adverse events: lidocaine or oral analogues versus placebo.*Trial has been published in abstract form. Data on adverse events for all patients receiving lidocaine regardless of dose are included and have been provided by Backonja (29). OR = odds ratio; CI = confidence interval.

7 studies, 4 provided information on adverse events in 185 patients. Ninety-four of these were treated with lidocaine or its oral analogues. Ninety-one were treated with an active control, including carbamazepine, morphine, amitriptyline, and gabapentin (36,40,41,47) (Fig. 4). Of the 94 patients treated with lidocaine or its oral congeners, 27 had adverse events, compared with 22 of 91 treated with active control drugs (OR: 1.23; 95% CI: 0.22 to 6.90; $P = 0.81$). Active control drugs produced a slightly less, but nonsignificant, likelihood of adverse events than lidocaine or oral analogues. However, the results are limited because of the small number of trials with adequate information on this end-point, and the heterogeneity of the model ($\chi^2 = 7.56$; $df = 3$; $P = 0.06$).

Discussion

Considerable debate now surrounds the young field of evidence-based medicine and many cautionary notes have been struck regarding the potential for misapplication of its methods (69). For example, meta-analysis of low quality reports may produce unreliable estimates of treatment effect (68,70,71).

Data from 19 randomized, placebo-controlled trials indicate that the analgesia resulting from the systemic administration of local anesthetics is superior to that from placebo. The main source of heterogeneity in the present meta-analysis was pain etiology. Other factors with the potential to produce heterogeneity, such as trial design, study quality, and time of outcome measurement, may have been present. We emphasize that the identification of heterogeneity in a meta-analysis does not necessarily undermine its conclusions.

The diverse etiologies of neuropathic pain may have a role in explaining heterogeneity, both clinical and statistical. Given the variability of etiologies, mechanisms, and presentations of neuropathic pain (72), an analogy can be drawn with headache as a symptom. The headache from a tumor may be mistaken at times for migraine or tension-type headache, and thus the symptomatic responses to identical treatments can differ. Lidocaine and its oral analog mexiletine relieved pain from diabetic polyneuropathy but were ineffective against plexopathy from tumor infiltration or HIV-related polyneuropathy. Though not conclusive, subgroup analyses to explore and explain heterogeneity suggest that neuropathic pain from diabetes, trauma, and cerebrovascular disease are more likely than pain of postinfectious etiology to respond. Systemic morphine and lidocaine were equally effective for postherpetic neuralgia (47) and postamputation stump pain (54) and both were superior to placebo. In the latter study, however, morphine was more effective than lidocaine for phantom pain (54). Tocainide (no longer marketed in the United States) appeared to be as effective as carbamazepine for trigeminal neuralgia (41). Future trials should restrict enrollment of patients to those with neuropathic pain of a single

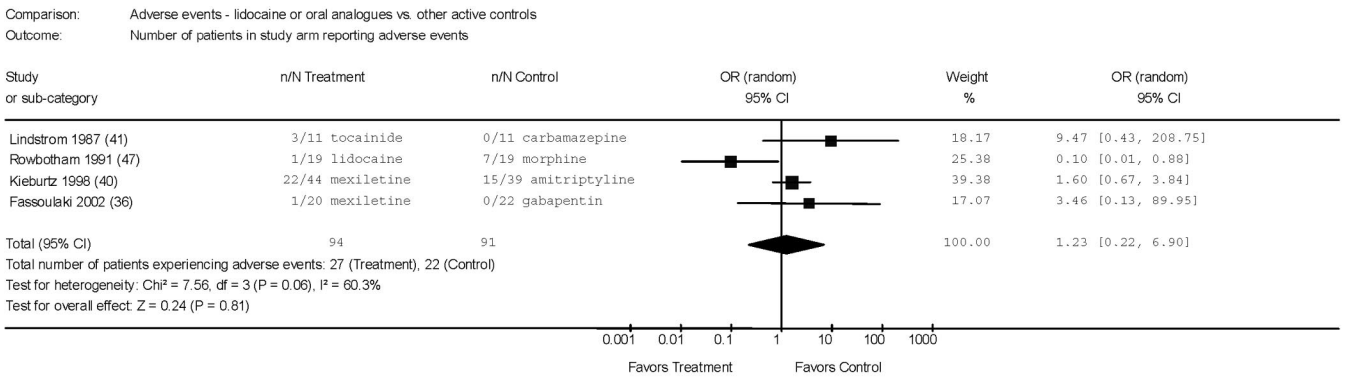

Figure 4. Comparison of adverse events: lidocaine or oral analogues versus other active controls. OR = odds ratio; CI = confidence interval.

etiology to clarify the interpretation of their findings. Even for a single entity (e.g., HIV/acquired immune deficiency syndrome neuropathic pain) it is unclear how well tolerated lidocaine or mexiletine are in malnourished patients with active systemic illness, but it is plausible that cachectic patients may be at increased risk for adverse events.

Our analyses show that the systemic administration of sodium channel blocking drugs can relieve pain in selected patients with neuropathic pain and that this effect is superior to placebo. A more difficult question to answer is whether a mean difference of 11 mm on a 0–100 scale (or 1.1 on a 0–10 numeric scale) represents a true clinical difference for patients. The analysis of continuous data from pain scales using central tendency measures (means or medians) is a mathematical attempt to make a multidimensional, subjective variable, 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 (73). Even in the absence of a frankly bimodal distribution, individual patients may experience a larger response. For other public health issues, e.g., arterial blood pressure reduction, it is accepted that small mean changes in systolic blood pressure across large populations can translate into significant improved clinical outcomes (74). One solution to this problem 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 (75). Several studies 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 from moderate-to-severe baseline pain intensity (0–10 scale) (73,76,77). We collected and analyzed the responder rates published in 14 of the mexiletine and lidocaine trials and found that these drugs were better than placebo (odds ratio: 2.04; 95% CI: 1.57 to 2.65, $P <$ 0.00001, data not shown). This result is in agreement with the WMD between oral anesthetics and placebo, and further suggests that such a difference is clinically important in the context of chronic neuropathic pain.

The analgesic effects of lidocaine and mexiletine were similar. However, lidocaine's short serum half-life of 120 min precludes the use of this drug for chronic use. Accordingly, pain relief with lidocaine has been measured within 24 h in all trials because in most patients the effect disappears a few hours after treatment. The mechanism of prolonged relief reported in animal models (78) and in some patients described in nonrandomized (6,79,80) and randomized studies (28,38,49) is still unknown. As discussed in a previous review (25), controlled studies are still required to determine the long-term effects of lidocaine on pain. A clinical approach might involve the chronic subcutaneous delivery of lidocaine via infusion pump but we are not aware of any randomized controlled studies using this technique. Despite its therapeutic limitations, lidocaine is likely to be used in future clinical trials as it is a prototypical blocking drug for tetrodotoxin-resistant sodium channels and one with which other novel, promising and more selective drugs can be compared.

In direct comparisons, the incidences of adverse events reported for lidocaine, tocainide, and mexiletine were similar to those for other active control drugs. Statistical heterogeneity, limited data, and diversity of drug classes in the comparison control groups limit external validity of the analysis of relative safety. However, indirect comparison of the incidences of adverse effects reported with lidocaine and mexiletine and those seen with gabapentin (a drug generally considered to have a good safety profile) in separate, controlled trials using similar pain models suggests a similar rate of occurrence (81,82). Across-trial differences in the definitions and methods to ascertain side effects precluded meta-analyses of the severity and nature of these adverse effects. It remains to be determined whether patients find the adverse

effects experienced with lidocaine and oral analogues to be less tolerable than those seen with other drugs used for neuropathic pain.

The precise role of lidocaine and its oral analogues in controlling neuropathic pain of differing etiologies is not yet fully established because of the multifaceted nature of neuropathic pain, the statistical and clinical heterogeneity of many of the trials, and the uncertainty of results from small studies. Well-structured, high-quality trials with active placebos or active drug controls, conducted according to uniform, and hence combinable, designs are needed to clarify the efficacy of these drugs in the treatment of neuropathic pain from specific etiologies. Future trials should also explore subcutaneous infusions and move from mexiletine to testing newer oral analogues with higher therapeutic ratios. In addition, growing interest in topically applied local anesthetics to treat acute (83,84) and chronic (85) pain suggests that there is a need to compare the benefits and harms of systemic versus topical local anesthetics for the relief of neuropathic pain from diverse etiologies.

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