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# *Intravenous Infusion Tests Have Limited Utility for Selecting Long-term Drug Therapy in Patients with Chronic Pain*

## *A Systematic Review*

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**Since the first description in the early 1990s, the scope of intravenous infusions tests has expanded to encompass multiple drug classes and indications. Purported advantages of these tests include elucidating mechanisms of pain, providing temporary relief of symptoms, and usefulness as prognostic tools in guiding drug therapy. In an attempt to discern the value of these tests, the authors conducted a systematic review to explore the rationale and evidence behind the following intravenous infusion tests: lidocaine, ketamine, opioid, and phentolamine. The studies evaluating all intravenous infusion tests were characterized by lack of standardization, wide variations in outcome measures, and methodological flaws. The strongest evidence found was for the intravenous lidocaine test, with the phentolamine test characterized by the least convincing data. Whereas intravenous opioid infusions are the most conceptually appealing test, their greatest utility may be in predicting poor responders to sustained-release formulations.**

INTRAVENOUS analgesic infusion tests have been used in a variety of contexts for almost 20 yr to facilitate the management of patients with chronic pain.[1–4] Initially designed as diagnostic tools to help elucidate the cellular mechanisms of nociception,[3,5] these brief and uncomplicated tests have experienced a recent resurgence as prognostic instruments used to predict analgesic response to specific classes of drugs. In the past two decades, intravenous formulations of phentolamine,[6] lidocaine,[7,8] several opioids,[9–11] propofol,[12] and ketamine,[13] have been used in various contexts to attempt delineation of pain mechanisms and prediction of subsequent response to oral analogues. Analgesic infusion tests have also been used to predict response to surgical interventions, specifically motor cortex stimulation.[14–16]

The rationale behind use of intravenous infusion tests is that they can quickly predict those patients who will respond to a subsequent course of oral medication, thereby eliminating the time and expense of a lengthy oral medication trial and reducing the risks of adverse effects associated with ineffective drug treatment. An infusion test can serve as a prognostic tool for a treatment associated with significant risk, such as implantable analgesic devices or oral opioid therapy.[14,17] In these situations, a screening test with a high specificity and positive predictive value may prevent patients unlikely to respond to a high-risk therapy from receiving an unwarranted treatment. Intravenous infusion tests can also provide valuable information when the definitive treatment provides considerable relief to only a small subset of patients. An example is the use of an intravenous lidocaine infusion to predict response to mexiletine, a drug associated with few responders (a high number needed-to-treat) and significant side effects (a low number-needed-to-harm).[18] In this circumstance, patients being considered for oral mexiletine might benefit from an intravenous screening test with a high sensitivity and negative predictive value, which would minimize the chances for a false-negative result, thereby identifying the patients most likely to respond to treatment with mexiletine. For an over-the-counter drug like dextromethorphan, which may offer significant benefit to a select group of patients but is not usually covered by third-party payers,[19] a quick and simple screening test with a high observed agreement could help identify the patients most likely to respond to this therapy. Other potential advantages of intravenous infusion tests include elucidating pain mechanisms that may guide development of future treatments, establishing target doses for drugs with a wide therapeutic index, and predicting side effects in those patients inclined to experience them.

Despite the growing body of literature on intravenous infusion tests, there has been no previous attempt to systematically review the available evidence. The purpose of this article is to provide readers with an evidence-based framework outlining the rationale and existing literature on previously described intravenous

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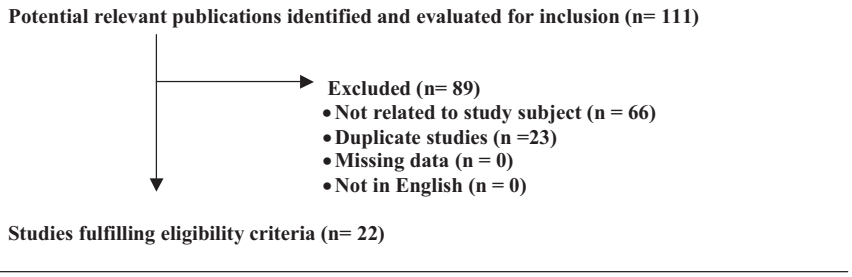


**Fig. 1. Flowchart demonstrating analysis of reviewed publications.**

infusion tests, along with informed conclusions regarding the validity and predictive value of these tests.

## Materials and Methods

*Search Strategy*

Articles reviewed were obtained *via* MEDLINE, EMBASE, and OVID search engines and through book chapters dating back to 1950. The databases were searched for the key words "intravenous infusion test," "intravenous lidocaine test," "intravenous ketamine test," "intravenous phentolamine test," and "intravenous 'opioid drug name' test." Cross references were then made between the drug name used to designate the infusion test (*e.g.*, lidocaine), and the terms "predictive" and "pain." Additional articles were obtained by cross-referencing the drug used in the infusion test with "pain" and various oral analogues (*e.g.*, "lidocaine AND mexiletine AND pain" or "phentolamine AND clonidine AND pain"). The bibliography sections of all articles used were then searched for pertinent references that might have been missed during the initial screening. Thereafter, the abstracts and methods sections of these articles were reviewed to determine whether or not any relationship could be ascertained between the response to one of the intravenous drugs being investigated and an oral analogue. In light of the paucity of data on this subject and wide variations in methodologies, techniques, outcome measures, and data presentation, all articles except solitary case reports were selected for systematic analysis.

*Search Results*

The search methods led to the identification of 111 articles. Among these, 89 were excluded because they were not related to the study subject or because they were duplicate publications/findings. The remaining 21 articles were analyzed, and their results are presented below. See figure 1 for the flow chart demonstrating the analysis of reviewed publications.

There are no validated scales by which to evaluate the quality of predictive intravenous infusion studies. Previously used scales for the evaluation of clinical studies[20,21] were adapted to create equivalent criteria that were then agreed upon by the three authors who used them to evaluate the articles in this analysis (see appendix). All articles were then evaluated using these criteria and assigned a score between 0 and 10 reflecting their methodologic quality.

*Statistical Analysis*

Sensitivity, specificity, positive predictive and negative predictive values of all test were extracted from various studies. Using these values, analysis was performed to calculate the median and interquartile range for the above categories. All analyses were done using STATA 9.2 (StataCorp LP, College Station, TX).

## Results

*Intravenous Lidocaine Test*

**Rationale and Background.** The pain-relieving properties of sodium channels blockers have been known for hundreds of years, dating back to the 17th Century, when European settlers described using coca leaves to alleviate toothaches.[22] The analgesic effect of systemic lidocaine was first reported in 1961, when Bartlett and Hutaserani[23] used an intravenous infusion to treat postoperative pain. Although effective, the high incidence of side effects at doses required for pain control coupled with the advent of many safer forms of analgesia led to a decline in its use over the ensuing decades. The 1980s witnessed resurgence in the analgesic use of systemic lidocaine after the publication of a report by Boas *et al.*[24] demonstrating that intravenous lidocaine attenuated central pain, a condition often refractory to more conventional treatment.

Voltage-gated sodium channels are heteromeric transmembrane protein complexes consisting of one very large $\alpha$ subunit and one or two smaller ancillary $\beta$ subunits. Among the 10 known channel isoforms, 9 have been cloned and are functionally expressed.[25,26] In the absence of any subtype-specific sodium channel antagonists, the various isoforms have traditionally been classified on the basis of their sensitivity to blockade by the puffer-fish toxin tetrodotoxin, a system that predates the identification of channel isoforms. Both tetrodotoxin-sensitive (Na 1.3 and 1.7) and -resistant (1.8 and 1.9) channels have been implicated in the etiology and maintenance of pain.

**Table 1. Studies Examining the Value of Intravenous Lidocaine Testing in Predicting Response to Subsequent Treatment in Patients with Chronic Pain**

| Author | Patients and Conditions | Quality Score, 0–10 Scale | Study Design | Treatment | Results and Comments |
|---|---|---|---|---|---|
| Attal,[7] 2004 | 22 pts with postherpetic neuralgia or nerve trauma | 9 | DB, PC with open-label f/u | Randomized to receive 2 infusions of 5 mg/kg lido IV or placebo; 2 weeks later, they received the other drug; 16 pts were then treated with oral mex (mean dose 737 mg/d) | Lido reduced spontaneous pain and mechanical allodynia, but not thermal allodynia, compared to placebo; percent relief of mechanical allodynia with lido correlated with mex relief; no pt who failed to respond to lido responded to mex; 14 of 16 pts stopped mex by 3 months because of SE or poor relief |
| Legroux-Crespel,[122] 2003 | 4 pts with erythromelalgia | 3 | Observational | 100–200 mg of lido IV infused followed by 200–600 mg/d mex | Paroxysmal flares improved in all pts by 3rd day and persisted for 2 yrs; evaluated combined therapy, not correlation |
| Trentin,[41] 2000 | 183 pts with central and peripheral neuropathic pain | 4 | Retrospective | 4 mg/kg lido IV followed by various sodium channel l blockers | 90% of lido responders had decreased pain with oral drugs, and 85% of nonresponders had no improvement; response rates were highest for Na+ channel blockers (carbamazepine 77% and mex 76%) than for amitriptyline (12%) and gabapentin (61%) |
| Sakurai,[40] 1999 | 30 pts with multiple sclerosis | 6 | Prospective, single-blind, PC | Received saline followed by 6–8.8 mg/kg lido in a blinded fashion, followed by lido maintenance; they then received 300–400 mg/d mex and placebo in blinded crossover fashion | Lido and mex showed excellent results and correlation for relief of painful seizures and paroxysmal pain and itch; lido but not mex reduced Lhermitte's sign |
| Ohara,[123] 1998 | 9 pts with spasmodic torticollis | 6 | Observational | Received saline followed by 100 mg of lido in blinded fashion, followed by 450–1,200 mg/d mex | Lido but not saline produced decreased dystonia and pain in all pts; all pts also experienced excellent reductions with mex lasting through 9 months f/u |
| Galer,[8] 1996 | 9 pts with peripheral neuropathic pain; 5 pts had diabetic neuropathy | 6 | Observational | DB IV lido infusions of 2 and 5 mg/kg in random order followed by 400–1,200 mg/d mex | Both lido doses reduced pain to similar degree; 3 of 3 pts with good relief from lido had good relief with mex; only 2 of 6 pts with poor relief from lido responded well to mex |
| Edmondson,[146] 1993 | 4 pts with central poststroke pain | 4 | Observational | 50–100 mg of IV lido followed by 1–4 mg/min for 48h; all pts then were put on mex | All pts had excellent relief with lido; 2 pts had excellent relief with 600 mg/d mex, and 2 pts had intolerable SE |
| Ichimata,[38] 2001 | 20 pts with postherpetic neuralgia | 4 | PC with open-label f/u | Single-blind IV glucose infusion followed by 2 mg/kg flecainide | 15 pts achieved significant benefit from IV flecainide and were titrated up to 200 mg/d oral flecainide; mean pain score decreased from 36 to 16 after 1 mo, with 14 of 15 pts responding to rx; response to IV flecainide greater in pts with shorter duration of pain; pts continued to receive concomitant rx, including nerve blocks, during dose titration |
| Agarwal, 2005* | 26 pts with postamputation pain | 7 | DB, PC, 2-phase crossover study | Double-blind IV lido (5 mg/kg), morphine, or placebo infusion on 3 consecutive days, followed by DB crossover study comparing oral agents | No correlation ($r = 0.15$) between IV lido and oral mex response; among 6 lido responders, 1 responded to mex; among 13 lido non-responders, 9 had a negative response to mex |
| Carroll,[130] 2008 | 37 pts with neuropathic pain | 6 | Retrospective | 37 IV lido responders out of 99 pts were prescribed mex | Analgesic response to IV lido predicted pt acceptance of oral mex; each 20% decrease in analgesic response to lido increased the rate of mex discontinuation by 30%; no outcome measures reported |

* Agarwal S, Tella P, Haythornthwaite J, Raja SN: Change in intensity of postamputation pain by intravenous infusion of lidocaine and morphine does not predict effectiveness of oral mexiletine and morphine. Presented at the 11th World Congress on Pain, Sydney, Australia, August 21–26, 2005.

DB = double-blind; f/u = follow-up; IV = intravenous; lido = lidocaine; mex = mexiletine; PC = placebo-controlled; pts = patients; SE = side effects.

The activation of voltage-gated sodium channels may play a role in the pathogenesis and maintenance of both neuropathic and inflammatory pain. A growing body of evidence suggests that the proliferation and activation of sodium channels after nerve injury and carrageenan-induced inflammatory pain may result in ectopic discharges stemming from the site of injury, dorsal root ganglia, or even in adjacent uninjured neurons.[27–30] Spontaneous discharges have been shown to develop in both myelinated and unmyelinated nerve fibers, suggesting that ectopic activity can arise in both nociceptors and low-threshold mechanoreceptors.[31] In addition to spontaneous pain, preclinical evidence also supports a role for both tetrodotoxin-sensitive and -resistant sodium channels in evoked pain.[32,33]

It is not surprising then that controlled clinical studies have demonstrated efficacy for systemic lidocaine and its oral congeners for neuropathic and acute nociceptive pain.[34–37] The plasma concentration of lidocaine necessary to relieve clinical and experimental pain is on the order of 5–10 $\mu$M, far less than that required to abrogate nerve conduction.[25] However, several factors limit the use of intravenous lidocaine and its congeners in clinical practice. First, it is impractical to give an intravenous infusion on a long-term treatment basis, and it is unclear whether repeated infusions result in prolonged pain relief. Second, intravenous lidocaine is associated with significant dose-related side effects including dizziness, sedation, tinnitus, and, in higher doses, seizures and arrhythmias. The use of mexiletine generally involves a long titration schedule, and is limited by a high incidence of nausea and sedation. The antiarrhythmics tocainide and flecainide, which have also been shown in clinical trials to be effective for neuropathic pain,[38,39] have been implicated in cardiac arrhythmia-related fatalities. Consequently, although a study demonstrated efficacy for oral flecainide in 15 patients with postherpetic neuralgia who responded positively to a blinded intravenous infusion,[38] these drugs are rarely used clinically.

**Intravenous Lidocaine Test Results.** There have been several attempts to evaluate the predictive value of intravenous lidocaine for treatment with its oral congener, mexiletine (table 1). Attal *et al.*[7] treated 22 patients with postherpetic neuralgia or nerve trauma with either a 5 mg/kg lidocaine infusion or saline in a double-blind, placebo-controlled crossover study. Sixteen patients were subsequently started on mexiletine 2 weeks after the second infusion regardless of their response. Eleven patients (50%) responded to lidocaine but not placebo, with at least a 50% decrease in spontaneous pain, and 12 patients (54%) obtained at least 33% pain relief. Lidocaine also significantly reduced brush allodynia and mechanical hyperalgesia compared to placebo, but not cold allodynia. The correlation between lidocaine and mexiletine response was strong for dynamic mechanical allodynia ($P < 0.01$, Kendall $\tau$ correlation coefficient 0.62) but weaker for spontaneous pain ($P = 0.06$, Kendall $\tau$ correlation coefficient 0.34). None of the four patients who failed to respond to lidocaine responded to mexiletine. The results of this study suggest that some symptoms may not be mediated by the proliferation of sodium channels, or that higher doses of sodium channel blockers are needed to attenuate them.

Sakurai *et al.*[40] performed a placebo-controlled crossover study in 30 patients with pain secondary to multiple sclerosis. After a blinded saline infusion, all patients received a 6–8.8 mg/kg bolus of lidocaine followed by a continuous infusion for an unspecified duration (mean serum levels 2.4 $\mu$g/ml). Patients then received 300–400 mg/d mexiletine or placebo in a crossover fashion. Among the 10 patients with painful tonic seizures who received lidocaine and mexiletine, all patients responded with complete relief to both drugs. In the 7 patients with paroxysmal pain and itch, 100% also obtained complete eradication of symptoms with both drugs. In the 12 patients with painful spontaneous electrical sensations (Lhermitte's sign), 83% responded with complete relief and 17% with moderate relief during the lidocaine infusion. However, only 2 of the 12 patients with these symptoms responded to mexiletine. Mexiletine blood levels were not drawn; therefore, one possible reason for this discrepancy is that the relatively low doses of mexiletine administered were subtherapeutic for treating this pain. Although all symptoms responded somewhat to lidocaine, a trend was noted whereby the constant neuropathic symptoms tended to be more resistant to the beneficial effects of lidocaine than intermittent symptoms.

Galer *et al.*[8] performed a double-blind study in which nine patients with peripheral neuropathic pain received blinded infusions of 2 mg/kg and 5 mg/kg intravenous lidocaine, followed by oral mexiletine. Both doses of lidocaine resulted in moderate pain relief, with no difference noted between doses. All three patients who responded with significant relief to lidocaine also responded to mexiletine treatment. Among the six patients who failed to respond to lidocaine, two obtained good relief with mexiletine. Unlike the study by Attal *et al.*,[7] no correlation was noted between lidocaine and mexiletine response for evoked pain.

Trentin *et al.*[41] conducted a retrospective study correlating the response to intravenous lidocaine to assorted oral analgesics in 183 patients with neuropathic pain. Overall, 90% of lidocaine responders experienced significant relief with oral drugs, whereas 85% of nonresponders failed to obtain significant relief. Although more patients responded to the oral sodium channel blockers mexiletine and carabamazepine than gabapentin and amitriptyline, the baseline differences in patients and the lack of standardization in treatment regimens preclude any definitive conclusions from being drawn.

Finally, Agarwal *et al.*§ randomized 26 subjects with neuropathic pain to receive either intravenous lidocaine, morphine, or placebo on three consecutive days. In the double-blind crossover phase, the same subjects received mexiletine, oral morphine, or oral placebo in 8-week treatment periods. No significant correlation was noted ($r = 0.15$) between pain relief with intravenous lidocaine and mexiletine.

*Intravenous Ketamine Test*

**Rationale and Background.** It is well-established that the excitatory amino acid glutamate is intricately involved in acute and chronic pain states. After tissue injury, the excitatory signals transmitted through afferent neurons in the spinal cord and periphery are mediated primarily *via* the fast-inactivating kainate and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) subtypes of the glutamate receptor. However, when painful stimuli of longer duration and greater intensity ensue, the accumulation of prolonged, slowly depolarizing action potentials, results in the removal of the tonic $Mg^{++}$ block from the *N*-methyl-D-asparate (NMDA) glutamate receptor.

Activation of the NMDA receptor (NMDA-R) enhances sustained neuronal depolarization, thereby contributing to increased excitatory transmission along afferent pain pathways in the dorsal horn of the spinal cord, a process known as wind-up. The NMDA-R has also been implicated as playing a key role in neuroplasticity, long-term potentiation, and opioid tolerance.[42–44] Prolonged activation of NMDA-R result in alterations in cellular signaling pathways that accentuate the responsiveness of nociceptive neurons, a phenomenon known as central sensitization. Prolonged NMDA-R stimulation can also lead to functional antagonism of opioid analgesic effects.

The NMDA-R complex is one of several ligand-gated ion channels that permit diffusion of sodium and potassium channels upon activation. Unlike other ionotropic glutamate channels, activation of NMDA-R also allows passage of calcium ions, which can affect intracellular signal processing.[45] The NMDA receptor ion channel is a heterotetrameric structure that consists of up to seven subunits.[46] These include a pore-forming NR-1 subunit that binds glycine, at least one glutamate-binding NR-2 subunit, and in some cases another glycine-binding NR-3 complex. Present within the various subunits are numerous allosteric binding sites that influence function, including a zinc binding site, a proton sensor, and a polyamine site that serves to shield the proton sensor when occupied. The binding site for magnesium lies within the ion channel and magnesium blocks receptor activation under resting conditions. Within the same ion channel, there is also a site that binds numerous noncompetitive antagonists used in clinical practice such as ketamine, dextromethorphan, amantadine, and memantine.

Clinical studies have evaluated the use of NMDA-R antagonists for a wide array of pain conditions. There appears to be moderate evidence supporting NMDA-R antagonists for preemptive analgesia before surgery,[47,48] mixed evidence for cancer-related pain,[19,49] and strong evidence for neuropathic pain.[43] Evaluating the efficacy of NMDA-R antagonists for chronic pain is difficult because most drugs in clinical use exert myriad effects outside of the NMDA-R complex, and similar pain conditions can be mediated by different mechanisms. For example, a double-blind, placebo-controlled crossover study found the NMDA-R antagonist dextromethorphan but not memantine, to significantly relieve pain from diabetic neuropathy; for postherpetic neuralgia, neither NMDA antagonist proved effective.[50]

Ketamine is the most effective and well-studied NMDA-R antagonist, but it is routinely available only in an intravenous formulation. There are several obstacles to the use of ketamine for chronic pain. These include low oral bioavailability, a lack of any available formulation for chronic delivery, concerns over psychomimetic side effects, and mixed efficacy in clinical trials.[51,52] These treatment pitfalls have led to interest in evaluating the ability of an intravenous ketamine infusion to predict subsequent response to an oral NMDA-R treatment regimen.[53,54] One question that arises when evaluating the predictive value of intravenous ketamine for subsequent oral NMDA-R antagonists is choosing the optimal dose and/or response rate. In animals, NMDA-R antagonists show indisputable evidence of antinociception after nerve injury, whereas the evidence for efficacy in inflammatory pain is less robust.[55–59] Yet, ketamine at high doses is capable of relieving all types of pain, not by virtue of its NMDA-R blocking properties, but because of its anesthetic and dissociative effects. Unlike lidocaine and its oral congener mexiletine, ketamine and other NMDA-R antagonists are in separate drug classes, and possess a wide array of different antinociceptive effects through means other than NMDA-R antagonism. These distinct properties pose a daunting challenge to the use of ketamine as a predictive response tool for other NMDA-R–blocking drugs and may predispose the tests to intrinsic inaccuracies.

**Intravenous Ketamine Test Results.** There have nevertheless been several attempts at using an intravenous ketamine infusion to predict response to an oral dextromethorphan treatment regimen (table 2). In a series of studies by Cohen *et al.*,[13,60,61] the authors examined the correlation between response to an intravenous ketamine infusion and intermediate-term relief with subsequent dextromethorphan in chronic pain patients with neuropathic pain, fibromyalgia, and opioid tolerance. In the first two studies, a detailed statistical

§ Agarwal S, Tella P, Haythornthwaite J, Raja SN: Change in intensity of postamputation pain by intravenous infusion of lidocaine and morphine does not predict effectiveness of oral mexiletine and morphine. Presented at the 11th World Congress on Pain, Sydney, Australia, August 21–26, 2005.

**Table 2. Studies Examining the Value of IV Ketamine Testing in Predicting Response to Subsequent Treatment in Patients with Chronic Pain**

| Author | Patients and Conditions | Quality Score, 0–10 Scale | Study Design | Treatment | Results and Comments |
|---|---|---|---|---|---|
| Cohen,[13] 2004 | 25 pts with neuropathic pain | 7 | Retrospective | All pts received blinded saline followed by 0.1 mg/kg ket infusions; regardless of response, pts were put on a DX titration scale (mean dose 202 mg/d) and followed 4–6-wk post-treatment | The optimal cutoff value for ket response to predict DX response was at least two-thirds pain relief; the sensitivity, specificity, PPV, and NPV of the ket test were 75%, 92%, 90%, and 80%, respectively; the observed agreement was 84%; there was no association between ket and DX side effects |
| Cohen,[60] 2006 | 34 pts with fibromyalgia | 7 | Observational | All pts received blinded saline and low-dose (0.25–0.5 mg) midazolam infusions followed by IV ket (0.1 mg/kg); regardless of response, pts were put on a DX titration scale (mean dose 166 mg/d) and followed 4–6 wk post-treatment | The optimal cutoff for a ket response was again two-thirds pain relief; the sensitivity, specificity, PPV, and NPV of the ket test were 83%, 86%, 77%, and 91%, respectively; the observed agreement was 83%; a correlation was noted between ket and DX side effects |
| Cohen,[61] 2008 | 56 opioid-tolerant chronic pain pts | 7 | Observational | All pts received blinded saline and low-dose (0.25 mg) midazolam infusions followed by IV ket (0.1 mg/kg). Regardless of response, pts were put on a DX titration scale (mean dose 211 mg/d) and followed 4–6 wk post-treatment. | The sensitivity, specificity, PPV, and NPV of the ket test were 72%, 68%, 52%, and 85%, respectively; the observed agreement was 78%; a correlation was noted between ket and DX side effects |
| Furuhashi-Yonah,[62] 2002 | 8 with chronic neuropathic pain | 5 | Randomized, PC | Pts who responded to an IV ket infusion (dose not noted) received either placebo or 0.5 mg/kg every 6 h oral ket | All pts obtained > 20% reduction in pain and allodynia (mean pain score declined from 77 to 49 in ket group vs. 79 to 68 in placebo group); 4 pts continued to experience long-term (> 9 mo) benefit with treatment |

DX = dextromethorphan; IV = intravenous; ket = ketamine; NPV = negative predictive value; PC = placebo-controlled; PPV = positive predictive value; pts = patients.

analysis determined the optimal cutoff for pain relief with the ketamine infusion to predict a positive response to dextromethorphan treatment was at least two-thirds pain relief, indicating that even the low-dose (0.1 mg/kg) ketamine infusion used may have been relatively more potent than high-dose dextromethorphan. Combining data from all three studies, the authors found overall sensitivity, specificity, positive predictive value, and negative predictive values of 76%, 78%, 67%, and 85%, respectively. The high negative predictive value indicates that only a small percentage of patients who will respond to dextromethorphan treatment will fail to respond to a screening ketamine infusion. In all three studies, the response to placebo infusion also predicted response to dextromethorphan treatment; in two of the studies, a significant correlation was noted between side effects to the two drugs.[60,61] One of the three studies was conducted in opioid-tolerant pain patients,[61] and a higher correlation between response to intravenous ketamine and subsequent response to oral dextromethorphan was found in subjects presenting with nociceptive than neuropathic pain and in those patients receiving low rather than high-dose opioid therapy. None of the three studies reported a sustained benefit from the low-dose, one-time ketamine infusion.[13,60,61]

In addition to using intravenous ketamine to predict response to dextromethorphan, there is one published study evaluating the efficacy of oral ketamine in 8 patients who positively responded to an intravenous infusion (dose and degree of response not noted). In a letter to the editor, Furuhashi-Yonaha *et al.*[62] randomized eight patients with chronic neuropathic pain to receive

either placebo or 0.5 mg/kg ketamine every 6 h. Compared to the placebo group, significant reductions in both spontaneous and evoked pain were noted after 7 days in the ketamine, but not the placebo group. Three of eight patients reported nondebilitating side effects, which included one patient with nightmares. Nine months after completing the study, four patients continued to report good pain relief with oral ketamine. The effectiveness of blinding was not noted in this study.

*Intravenous Opioid Test*

**Rationale and Background.** Opioids have been used widely for their analgesic properties for over 5,000 yr.[63] Opioids exert their analgesic actions through inhibition of target cell activity. Mediating these effects are three endogenous opioid receptors, $\mu$, $\Delta$, and $\kappa$. Although peripherally located opioid receptors may play a role in the palliation of pain in certain contexts,[64] the predominant analgesic sites are believed to reside in the central nervous system. Some of the proposed mechanisms of cell inhibition include membrane hyperpolarization *via* the activation of potassium channels, suppression of voltage-gated calcium channels resulting in decreased terminal release of neurotransmitters, and receptor-mediated inhibition of adenylate cyclase.

Neuropathic pain was once considered resistant to opioid therapy,[65–67] but more recent studies have demonstrated efficacy for all types of pain conditions, albeit in different dose ranges.[68–70] Yet opioid therapy is not devoid of risks. There is strong evidence that opioids are effective for providing short-term pain relief in nearly any type of painful condition; however, there is only weak and inconsistent evidence supporting the efficacy for long-term pain reduction and/or functional improvement when chronic opioid therapy is used to treat noncancer pain.[71–74] Perhaps more concerning is the observation that between one-fourth and one-half of pain patients will develop one or more aberrant behaviors, and between 5% and 15% will show some evidence of addiction.[73–78] In a meta-analysis by Kalso *et al.*,[72] the authors calculated the number needed to harm as 4.2. These sobering statistics have led several experts to advocate investigating intravenous infusions to assess responsiveness to opioid therapy.[17,79]

**Intravenous Opioid Test Results.** Efforts to evaluate the ability of an intravenous opioid infusion to predict response to an oral opioid treatment course have yielded mixed results at best (table 3). In a double-blind, placebo-controlled crossover study, Attal *et al.*[80] treated 15 patients with central pain after stroke or spinal cord injury with an intravenous morphine infusion titrated to the maximum tolerated dose followed by an open-label course of oral treatment. Seven patients responded with at least 50% pain relief, and eight failed to respond to therapy. The effects of intravenous morphine were significantly greater on brush-induced allodynia than they were for spontaneous pain or mechanical hyperalgesia. Among the seven patients in each group available for follow-up, no morphine nonresponder continued on oral morphine therapy after 6 months *versus* four responders who continued therapy. Twelve months after commencing opioid therapy, three of these patients continued to report significant benefit. In the oral opioid treatment phase, six patients stopped treatment within 2 weeks because of unacceptable side effects, and four patients dropped out after 1 month because of inadequate pain relief.

Two studies found similar results when evaluating opioids for postamputation pain. In a double-blind, placebo-controlled crossover study evaluating opioids for phantom limb pain, Huse *et al.*[11] found 42% of patients responded with greater than 50% pain relief during a 4-week oral morphine treatment period *versus* 8% who responded to placebo administration. Yet, a linear regression analysis revealed that an intravenous infusion test performed before the oral treatment phase showed no predictive value for subsequent treatment with the same drug. Agarwal *et al.*§ conducted a double-blind, placebo-controlled, 2-phase crossover study comparing the responses to intravenous lidocaine, morphine, and placebo, with their oral analogues. The authors also found no significant correlation ($r = 0.24$) between the response to intravenous and oral morphine after the double-blind oral titration phase, whereby subjects received 8-week treatment with mexiletine, placebo, or oral opioids in crossover fashion. In contrast to Attal *et al.*,[80] 9 of 10 nonresponders to intravenous morphine obtained at least 50% pain relief with the continuous-relief oral formulation.

Finally, Dellemijn *et al.*[9,10] assessed the correlation between intravenous and transdermal fentanyl response in two separate manuscripts. In the first, a randomized, double-blind, active placebo-controlled study conducted in 53 patients with neuropathic pain found that intravenous fentanyl provided superior analgesia (66% relief) compared to diazepam (23% relief) and saline (12% relief). In an open-label follow-up study, 13 of 48 patients obtained substantial and 5 obtained moderate pain relief during a 12-week treatment period with transdermal fentanyl. After 2 yr of transdermal fentanyl treatment, pain relief continued to be at least moderate in only six patients. Similar to the study by Attal *et al.*, a negative response to the intravenous infusion strongly predicted a poor response to transdermal fentanly (92% negative predictive value). The correlation coefficient between percent pain relief from the intravenous infusion and transdermal treatment protocol at 12-week follow-up was 0.59, indicating a modest association.

*Intravenous Phentolamine Test*

**Rationale and Background.** Autonomic nervous system dysfunction frequently accompanies chronic pain. Although complex regional pain syndrome is the most well-known pain disorder associated with sympathetic

**Table 3. Studies Examining the Value of IV Opioid Testing in Predicting Response to Subsequent Treatment in Patients with Chronic Pain**

| Author | Patients and Conditions | Quality Score (0–10 Scale) | Study Design | Treatment | Results and Comments |
|---|---|---|---|---|---|
| Dellemijn,[9,10] 1997–8 | 48 pts with neuropathic pain who took part in a previous DB, PC crossover trial | 7 | Open-label prospective study in pts who participated in a DB, PC trial comparing IV fentanyl, diazepam, and saline | 53 pts received either IV fentanyl (5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and diazepam (0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or fentanyl and saline in random order; 48 pts then took part in an open-label study evaluating transdermal fentanyl (mean dose 45 $\mu g/h$) for 12 weeks | In the DB, PC study, fentanyl (66% relief) > diazepam (23%) > saline (12%); a significant correlation was found between pain reduction during the IV fentanyl infusion and transdermal treatment phase |
| Huse,[11] 2001 | 12 pts with phantom limb pain | 8 | DB, PC, crossover | Before treatment with oral MSO4 or placebo, pts received an IV infusion of MSO4 (20 mg/h MSO4) or saline, followed by a 4-week treatment period; pts who responded to IV MSO4 were included in trial | Neither IV MSO4 nor saline predicted response to oral treatment with MSO4 (range 70–300 mg/d) or placebo; in the oral phase, MSO4 was superior to placebo for phantom pain |
| Attal,[80] 2002 | 16 pts with central pain | 8 | DB, PC, crossover with open-label follow-up | After an open phase when all pts received IV morphine, they were randomized to blinded IV infusions of maximally titrated MSO4 (mean 16 mg) or saline in a crossover fashion; all pts were then started on oral MSO4 | Among the 15 pts who completed the study, 7 responded to IV MSO4 and 8 did not; among responders, 4 of 7 continued on oral MSO4 after 6 months and 3 after 12 months (mean 93 mg/d); among nonresponders, none continued oral MSO4 after 6 months |
| Agarwal, 2005* | 26 pts with postamputation pain | 7 | DB, PC, 2-phase crossover study | Double-blind IV morphine (0.05 mg/kg), lidocaine, or placebo infusion on 3 consecutive days, followed by DB crossover study comparing oral agents | No significant correlation ($r = 0.24$) between IV and oral MS04 response; among 13 IV MS04 responders, 8 responded to oral MS04; among 10 IV nonresponders, only 1 had a negative response to oral MS04 |

* Agarwal S, Tella P, Haythornthwaite J, Raja SN: Change in intensity of postamputation pain by intravenous infusion of lidocaine and morphine does not predict effectiveness of oral mexiletine and morphine. Presented at the 11th World Congress on Pain, Sydney, Australia, August 21–26, 2005.

DB = double blind; IV = intravenous; MSO4 = morphine sulfate; PC = placebo-controlled; pts = patients.

nervous system pathology, there are many other conditions whereby the interruption of sympathetic pathways may alleviate symptoms, including central and peripheral neuropathic pain, orofacial pain, fibromyalgia, cancer, pancreatitis, and phantom pain.[2,81–86] Collectively, painful conditions that respond to attenuation of sympathetic nervous system activity are termed sympathetically maintained pain (SMP). There are several mechanisms by which derangements in the sympathetic nervous system can act to induce, maintain, or worsen chronic pain. These include enhanced sensitivity of injured sensory nerves to circulating and endogenously released catecholamines,[87,88] increased expression of $\alpha$-1 adrenoreceptors on primary afferent nociceptors,[89,90] and hyperalgesic skin of complex regional pain syndrome patients,[91] central sensitization rendering A-$\beta$ mechanoreceptors algogenic,[92] and enhanced discharge and sympathetic sprouting in the dorsal root ganglia.[93,94] In some patients with complex regional pain syndrome, a reduction in sympathetic activity has been found.[95]

The diagnosis of SMP is most frequently made by a positive response to sympathetic blockade. Yet, in addition to containing inherent risks, the sensitivity of sympathetic ganglia blockade to ascertain a possible sympathetic component may be undermined by the spread of local anesthetic to somatic nerves and systemic absorption, both of which may alleviate neuropathic pain.[96–98] This realization has led to the use of an intravenous phentolamine infusion as a means to diagnose SMP.[99] In studies comparing sympathetic blockade of the upper or lower extremities to intravenous phentolamine tests, Dellemijn *et al.*[100] and Wehnert *et al.*[101] both found a

**Table 4. Studies Examining the Value of IV Phentolamine Testing in Predicting Response to Subsequent Treatment in Patients with Chronic Pain**

| Author | Patients and Conditions | Quality Score (0–10 Scale) | Study Design | Treatment | Results and Comments |
|---|---|---|---|---|---|
| Phillips,[147] 2006 | 37-year-old woman with idiopathic gastroparesis and abdominal pain | 4 | Case report | Pt received > 80% pain relief after 0.5 mg/kg IV phentolamine; pt reported significant relief and opioid reduction 2 months after she was started on 0.2 mg/d clonidine | Pain scores and long-term follow-up not noted on clonidine |
| Byas-Smith,[102] 1995 | 41 pts with diabetic neuropathy | 7 | Phase 1: DB, PC, 3-phase crossover; Phase II: DB, PC, 3-phase crossover, followed by a blinded IV phentolamine test in CR | Pts received in a double-blind fashion transdermal clonidine (0.1–0.3 mg/d) or placebo; all responders then enrolled in second 3-phase crossover DB, PC study to identify CR; CR then underwent IV phentolamine test | 12 or 41 pts responded positively to clonidine but not placebo in phase I and 8 of 12 to phase II (CR); none of the 3 CR tested obtained significant relief with either saline or phentolamine infusion; all 8 responders obtained benefit from continued transdermal clonidine for up to 3 mo |
| Davis,[6] 1991 | 6 subjects with neuropathic pain and hyperalgesia | 5 | Open-label prospective study | 4 of 6 pts diagnosed with SMP by sympathetic ganglia block (n = 6) and phentolamine test (n = 5); 0.2 or 0.3 clonidine patches applied consecutively to hyperalgesic skin | All 4 pts with SMP experienced significant reductions in hyperalgesia with clonidine *vs.* 0 of 2 pts with sympathetically independent pain; injection of treated area with intradermal norepinephrine elicited hyperalgesic recurrence in a pt with SMP, but not in 4 control subjects |
| Arner,[3] 1991 | 104 patients with reflex sympathetic dystrophy, including 54 children | 6 | Observational study | 51% of pts obtained a marked reduction in spontaneous and evoked pain after 5–15 mg of IV phentolamine; all pts subsequently were treated with 5–30 mg of IV regional guanethidine on one or more occasions | All 53 pts with a (+) IV phentolamine test responded to guanethidine *vs.* 49% of negative responders; children received lower doses of guanethidine under general anesthesia; mean duration of pain relief in responders was 3.9 weeks |

CR = consistent responder; DB = double-blind; f/u = follow-up; IV = intravenous; PC = placebo-controlled; SMP = sympathetically maintained pain.

phentolamine infusion to be a more specific, but less sensitive means of diagnosing SMP.

**Intravenous Phentolamine Test Results.** There have been two attempts to correlate the pain relief obtained with an intravenous phentolamine test to the analgesia obtained by a prolonged treatment course with a sympatholytic agent (table 4). In the first open-label prospective study, Davis *et al.*[6] subjected six patients with reflex sympathetic dystrophy to sympathetic ganglion blocks and intravenous phentolamine infusions to identify those with SMP. In all patients, a clonidine patch was applied to the hyperalgesic skin. In each of the four patients diagnosed with SMP, application of the clonidine patch significantly reduced cold and mechanical hyperalgesia. In three of these patients, the beneficial effects were confined to the area beneath the patch, suggesting a purely peripheral effect. In none of the cases was touch threshold affected, a finding that argues against any local anesthetic effect. In the two patients with sympathetically independent pain, topical clonidine failed to relieve pain or reduce allodynia in the hyperalgesic area.

In a subsequent double-blind, placebo-controlled study, Byas-Smith *et al.*[102] treated 41 patients with diabetic neuropathy with either a transdermal clonidine or placebo patch. Among the 12 first responders, 8 were identified as consistent clonidine responders after a subsequent "enriched enrollment" stage consisting of a second placebo-controlled crossover study. Six of the eight consistent responders returned on a separate date for an

**Table 5. Oxford Centre for Evidence-based Medicine: Levels of Evidence and Grades of Recommendation**

| Level | Source of Evidence | Grade | Strength of Recommendation |
|---|---|---|---|
| 1a | Systematic review with homogeneity of RCTs | A | Consistent level I studies. Good evidence suggests that the benefit of the test substantially outweighs the potential risks |
| 1b | Individual RCT with narrow confidence interval | | |
| 1c* | All or none case series | | |
| 2a | Systematic review with homogeneity of cohort studies, or controlled trial without randomization | B | Consistent level 2 or 3 studies (or extrapolation from level 1 studies); fair evidence suggests the benefits of the test outweigh the potential risks |
| 2b | Low-quality RCT, well-designed clinical trial without randomization, or individual cohort study | | |
| 3a | Systematic review with homogeneity of case-control studies | | |
| 3b | Individual case control study | | |
| 4 | Case series | C | Level 4 studies (or extrapolation from level 2 or 3 studies); fair evidence exists that there are benefits to the test, but the balance between the benefits and risks are too close for making general recommendations |
| 5 | Expert opinion or based on preclinical research | D | Level 5 evidence (inconclusive/ inconsistent studies of any level); fair evidence that the risks of the test outweigh the potential benefits |

* Met when all patients died/experienced a negative outcome before the treatment became available, but some now survive/experience a positive outcome on it; or when some patients died/experienced a negative outcome before the treatment became available, but none now die/experience a negative outcome on it.

RCT = randomized controlled trial.

Available at: http://www.cebm.net/index.aspx?o=1025; accessed April 8, 2009. Adapted with permission.

intravenous phentolamine infusion, but three of these subjects could not be tested because of the absence of pain. Among the three consistent responders who did undergo a blinded intravenous phentolamine test, none responded with significant pain relief.

Phentolamine infusions have also been used to predict response to single-shot or serial intravenous regional analgesia. In an observational study, Arner[3] attempted to use the intravenous phentolamine test to predict response to administration of intravenous regional guanethidine, a postganglionic adrenergic blocking agent, in 104 patients with reflex sympathetic dystrophy. Among the 53 phentolamine responders, all obtained relief after regional guanethidine treatment. In the 51 nonresponders or "undecideds," 25 experienced excellent or partial relief after guanethetidine Bier blocks, *versus* 26 who experienced no relief. Guanethidine infusions were repeated on an "as needed" basis after pain recurred in patients who experienced complete or partial pain relief.

**Data Synthesis.** Synthesizing data with widespread variability in methodologies, techniques, drug and dosing regimens, follow-up periods, presentation, and outcome measures is fraught with potential inaccuracies. The only infusion test in which the methods, techniques, and outcome measures were standardized was the intravenous ketamine test. However, none of these three studies were blinded, none utilized a placebo oral treatment phase, the follow-up periods were relatively short, all studies were conducted at one institution, and the patient population (*i.e.*, department of defense beneficiaries) that participated in these studies may not be widely generalizable. Although an attempt was made to combine data for all infusion tests, caution must be exercised when interpreting and extrapolating the results.

Table 5 delineates the sensitivity, specificity, positive predictive value, and negative predictive value for each of the four intravenous infusion tests evaluated. Each value represents the median based on the results of all studies wherein a number could be calculated.

## Discussion

This systematic review demonstrates that, despite widespread use, most intravenous analgesic infusion tests have been inadequately studied to draw definite conclusions regarding their utility in predicting subsequent response to treatment. The available data are strongest for the intravenous lidocaine test and suggest that pain relief during a brief intravenous infusion of lidocaine is predictive of subsequent response to oral mexiletine. The purely open-label data for the intravenous ketamine test provide only limited evidence that pain relief during a brief intravenous infusion of ketamine can be used to predict subsequent response to oral dextromethorphan. Use of intravenous opioid tests does not appear to be of any value in predicting subsequent response to treatment with oral opioids. The limited data examining the use of the intravenous phentolamine test are conflicting, and there is no evidence to suggest that pain relief during a brief intravenous infusion of phentolamine can be used to predict response to subsequent treatment with oral or transdermal clonidine. On the basis of adapted

**Table 6. Overall Sensitivity, Specificity, and Predictive Value of IV Testing for Lidocaine, Ketamine, Opioids, and Phentolamine Based on the Available Evidence**

| Test (Number of Studies) | Median Sensitivity, (IQR) (Range) | Median Specificity, (IQR) (Range) | Median Positive Predictive Value, (IQR) (Range) | Median Negative Predictive Value, (IQR) (Range) | Levels of Evidence | Strength of Recommendation | AWP of Monthly Medication‖ |
|---|---|---|---|---|---|---|---|
| IV lidocaine (n = 6)* | 100% (89–100%) (20–100%) | 72% (47–90%) (29–100%) | 55% (20–83%) (17–100%) | 68% (40–85%) (12–100%) | 2b | B | $15# |
| IV ketamine (n = 3)† | 76% | 78% | 67% | 85% | 3a | B–C | $50** |
| IV opioids (n = 4)‡ | 66% (49–91%) (50–100%) | 72% (44–75%) (17–77%) | 52% (40–60%) (33–62%) | 90% (49–96%) (10–100%) | Evidence conflicting | D | $23†† |
| IV phentolamine (n = 3)§ | 68% (0–100%) (0–100%) | 70% (40–100%) (40–100%) | 62.5% (25–100%) (25–100%) | 75.5% (51–100%) (51–100%) | Evidence lacking | D | $151‡‡ |

Sensitivity is a statistical measure of how accurately the diagnostic block correctly identifies positive responders. Specificity is a statistical measure of how accurately the diagnostic block correctly identifies negative responders. Positive Predictive Value is the proportion of patients with a positive diagnostic infusion who positively respond to the oral medication. Negative Predictive Value is the proportion of patients with a negative diagnostic infusion who fail to respond to the oral medication. Numbers based on median values for all studies whereby data was available except for thee IV ketamine test, whereby data was combined because of identical methodologies. For IV lidocaine test, NPV and specificity are based on three studies. For the study by Sakurai and Kanazawa,[40] two separate values were used to calculate the median number denoted, one for paroxysmal pain and the other for Lhermitte's sign. For IV phentolamine test, the two studies for clonidine and one for guanethidine were combined. Levels of evidence and strength of recommendation based on Oxford Centre for Evidence-Based Medicine guidelines (table 5).

* Positive response for lidocaine and mexiletine defined as at least 50% in five of six studies. † Positive response for ketamine and dextromethorphan defined as at least 67% and at least 50%, respectively. ‡ Positive response for IV morphine and sustained-release opioid treatment defined as more than 50%; includes raw (unpublished) data from Huse *et al.*[11] § Positive response to IV phentolamine test and clonidine or guanethedine based on patient subjective report. ‖ Approximate cost paid by Johns Hopkins and Massachusetts General Hospitals Departments of Pharmacy as of February 15, 2009. # Based on 750 mg/d mexiletine. ** Based on 1 mg/kg dextromethorphan three times per day, contained in concentrated liquid. †† Based on 90 mg/d generic sustained release morphine. ‡‡ Based on four weekly 0.2-mg clonidine patches.

AWP = average wholesale price; IQR = interquartile range; NPV = negative predictive value.

guidelines provided by the Oxford Centre for Evidence-Based Medicine, the levels of evidence and strength of recommendation for each intravenous infusion test are listed in table 6.

The difficulty in synthesizing data and drawing conclusions is perhaps best illustrated by the scant literature (n = 21) analyzed despite liberal inclusion criteria that incorporated non-English articles, case series, and manuscripts with heterogeneous designs, quality and outcome measures. The manifold diagnoses contained in these studies might be construed by some as undermining the internal validity of this review; when viewed from a different perspective, it also highlights the conceptual appeal of intravenous drug testing. Almost all studies examining pharmacological therapy for chronic pain have selected patients on the basis of etiology (*i.e.*, diagnosis), and treatment results have mostly been disappointing (the numbers needed to treat typically range from just above 2 to greater than 8).[18,103,104] However, most experts now concur that mechanistically based pain treatment is likely to be more efficacious than etiologically based treatment, which presupposes multifarious pathophysiological factors, despite the inherent challenges in identifying underlying causation.[105,106] Although identifying pain mechanisms forms the theoretical foundation for intravenous drug testing, the widely disparate and underwhelming outcomes reported in these studies highlight the challenges involved in translating theory into practice.

Two confounding factors that warrant mention are the influences the placebo effect and psychosocial factors may have in prognostic infusion trials. The placebo effect is widely acknowledged to play a major role in clinical trials evaluating pain treatments.[107–109] The extent of this effect is predicated on multiple factors, including but not limited to classic conditioning, cognitive and psychological factors, and patient and physician expectations.[107,108,110–112] A placebo response has been shown to be more robust for procedures (*i.e.*, infusion tests) than pharmacotherapy, which may have implications for the current review.[113] In several of the studies analyzed, patients were selected for definitive therapy on the sole basis of their response to intravenous testing,[11,38,62] which could have magnified the influence of expectations on outcomes. When designing future intravenous infusion test studies, investigators might minimize the effects of expectation bias and placebo response by blinding all patients to the results of the infusion test. Among the studies included in this analysis, only two blinded all patients for both the intravenous and definitive treatment phases.[40]§

A second shortcoming revolves around the lack of emphasis on psychosocial factors during both the screening phase and as a treatment outcome. Numerous studies conducted in myriad pain conditions have found coexisting psychosocial factors to be a major determinant of prognosis.[114–116] Although several evaluated studies did exclude patients with serious psychiatric illness,[7,11,13,60,61,80] only two evaluated psychological indices as an outcome measure.[9,11] Psychological wellbeing is widely acknowledged to be one of the core outcome domains of chronic pain clinical trials[117];

therefore, future investigations should endeavor to include emotional outcome measures.

*Iintravenous Lidocaine Testing*

There is strong clinical and preclinical evidence that systemic lidocaine in a wide range of dosages relieves neuropathic pain.[25,118,119] There is moderate evidence in the form of preclinical and experimental studies that lidocaine relieves nociceptive pain.[25,120,121] On the basis of the extant literature, there appears to be a modest correlation between pain relief for lidocaine and its oral analogue mexiletine to treat neuropathic pain.[7,8,40,41] The correlation between lidocaine and sodium channel blockers is stronger than for other drugs used to treat neuropathic pain.[41] The correlation between lidocaine and mexiletine also appears to be stronger for paroxysmal pain than Lhermitte's sign. There is only weak evidence that the response to intravenous lidocaine can predict response to mexiletine for nociceptive pain.[122,123] Although animal studies have reported long-term benefit after systemic lidocaine,[124–126] the evidence for sustained pain relief in humans in extremely weak.[127]

Whereas the evidence suggests that the intravenous lidocaine test can be effectively employed to select patients with neuropathic pain who are most likely to respond to subsequent treatment with oral mexilitene, the long-term effectiveness of mexiletene therapy remains in question as a result of its significant side effect profile. A recent meta-analysis examined the use of systemic local anesthetics to relieve neuropathic pain and concluded that lidocaine and mexiletene were safe drugs for neuropathic pain, were superior to placebo, and were as effective as other analgesics.[128] However, the available data on adverse effects were limited and pooled in such a way that the frequency of individual side effects could not be discerned. Subsequent authors have warned that despite the apparent utility of these agents gleaned from the statistical combination of trials reported, the clinical utility of these agents may be very limited for the long-term treatment of neuropathic pain.[129] Indeed, a recent study employed survival analysis to identify factors predictive of clinical success during treatment of neuropathic pain with oral mexiletene.[130] Greater pain reduction during infusion of intravenous lidocaine predicted continued use of mexiletine during a subsequent course of oral therapy. However, despite claims of efficacy, the tolerance of mexiletine therapy was poor. Only 20% of subjects continued to take mexiletine more than 1 yr after initiating therapy, with the median time to discontinuation being 43 days. Thus, the true clinical utility of the intravenous lidocaine test awaits the availability of oral local anesthetic congeners that are better tolerated during chronic treatment.

*Intravenous Ketamine Testing*

There are several flaws in the studies evaluating the use of intravenous ketamine to predict treatment response to oral dextromethorphan.[13,60,61] These include the short follow-up period, the use of only a single dose of ketamine (0.1 mg/kg), and the absence of any control treatment group that received a non-NMDA receptor antagonist after ketamine infusion. Nevertheless, the studies that do exist provide weak evidence supporting the use of a ketamine infusion test to predict short-term treatment response to dextromethorphan therapy for both neuropathic and nociceptive pain. Future studies should be designed to assess the optimal dose of ketamine, the long-term response to dextromethorphan therapy in positive responders, and whether the response to ketamine can be used to predict therapeutic benefit from other NMDA receptor antagonists.

*Intravenous Opioid Testing*

The results of published and unpublished observations provide scant evidence for the use of IV opioids to predict subsequent response to an oral or transdermal treatment regimen.[9–11,80]§ Although the negative predictive values exceeded 90% in two studies,[10,80] both studies conducted in amputees found a very poor correlation between intravenous and continuous release morphine.[11]§ Part of the problem with using intravenous infusions to predict response to sustained-release opioid treatment is that more than 80% of patients who do not continue on long-term opioid treatment cease therapy not because of poor short-term analgesia, but secondary to adverse effects that may manifest over several weeks or months, such as constipation, dizziness, and somnolence.[131] Even in the two studies whereby a correlation was found between intravenous and oral treatment response,[10,80] only a small percentage of patients reported sustained benefit lasting at least 6 months.

However, on the basis of the extant literature, a good intermediate-term response to opioids is likely to be sustained for the long-term. In those patients who report significant benefit from opioid therapy 6 months after initiation of treatment, over 60% will continue to experience long-term benefit.[74,132–134] One study conducted in subjects with noncancer pain revealed that most patients with nonmalignant pain who fail an opioid trial are identified within 1 month.[135] Despite the strong conceptual foundation for developing a predictive tool for long-term opioid therapy, the widespread methodological flaws that pervade the existing studies and the large disparities in results preclude the routine usage of intravenous opioid testing without further investigation.

*Intravenous Phentolamine Testing*

Although the intravenous phentolamine test was the earliest infusion test described, there is less literature on this test than for the others. In part, this may be a

result of the ease of performing sympathetic ganglia blocks, which are quicker to perform and entail higher reimbursement rates. When the small results of the two studies are combined and analyzed, they yield conflicting results that do not justify the routine use of this time-consuming test as a predictive response instrument. Unlike lumbar sympathetic and stellate ganglion blocks,[136,137] a one-time infusion with phentolamine does not appear to provide sustained analgesic benefit to responders lasting longer than 12 h (peak effect 1–2 h).[3,99,100]

There are several observations that may help to explain the seeming discrepancies in the usefulness of intravenous phentolamine testing. First, none of the three studies analyzed documented the temperature rise in the affected extremities after the intravenous phentolamine test, which is necessary to confirm a technically successful test. In previous studies evaluating sympathetic bocks, a minimal temperature rise of at least 1°C has been used to document a sympathectomy,[138,139] although much greater temperature changes are often noted in cool extremities. Second, whereas Davis *et al.*[6] applied the clonidine patch over the area of hyperalgesic skin, the patch was not applied to the affected areas, which were presumably much larger, in the Byas-Smith study.[102] Even among the four responders in the former study,[6] the relief of hyperalgesia in three patients was confined to the skin region beneath the patch. This suggests that the peripheral effect of transdermal clonidine may be more relevant than the central effect with regard to analgesia, a finding supported by both preclinical and clinical studies.[140,141] Finally, in only one of the three studies were patients selected on the basis of presence of autonomic dysfunction.[6] In addition to its attenuating effect on sympathetic outflow, other proposed mechanisms for the analgesic effects of clonidine include antiinflammatory properties, local anesthetic effects, reduction in nerve conduction velocity, sedative properties, and synergistic actions with other analgesic agents.[142] In clinical trials, clonidine has been shown to reduce pain in a wide range of sympathetically independent conditions, including peripheral neuropathy, migraine headaches, and cluster headaches.[143–145] Thus, the relief of pain with clonidine does not presuppose a sympathetically based component, nor does the lack of response to an intravenous phentolamine test rule out SMP.

In the study evaluating the use of intravenous phentolamine to predict response to intravenous regional guanethidine treatment,[3] the criteria for a positive response to phentolamine included a marked reduction of both spontaneous and evoked pain, suggesting a higher threshold for a positive response. Fifty-four percent of the patients in this study were children, who tend to have a more benign and self-limiting course than adults. Repeated intravenous Bier blocks requiring extensive monitoring may also be associated with greater patient expectations than a medication trial. Whereas all 53 patients who responded to intravenous phentolamine also responded to one or more infusions of intravenous guanethidine, the observation that 49% of the nonresponders also experienced significant pain relief with the intravenous regional anesthesia limits the utility of this test. In summary, there is no credible evidence that the response to an intravenous phentolamine infusion reliably predicts response to pharmacological sympathetic blockade, and only weak evidence supporting the use of intravenous phentolamine before intravenous regional guanethidine.

### *Cost-effectiveness*

No one-time intravenous infusion test has been shown to provide consistent, long-term benefit[13,14,60,61,99,100,127]; therefore, the key question that must be asked for those tests that do have proven prognostic value is whether or not they are cost-effective. But this question cannot be answered because the variables that must be factored into this equation (*i.e.*, positive and negative predictive value, professional and facility fees paid, medication costs, anticipated duration of benefit, cost of alternative treatment for negative tests, *etc.*) either cannot be calculated with the available data or vary dramatically. As of February 15, 2009, the Medicare reimbursement rate for a less than 1 h of intravenous infusion was $128.62 in a hospital outpatient setting (all facility fee, no professional fee) and $68.89 in a physician office setting (all professional fee + $53 for up to 5 mg of phentolamine). Ironically, the tests that purport to prognosticate response to the most expensive medications (*i.e.*, nongeneric sustained-release opioids and clonidine patches) have the least proven benefit, whereas the most predictive infusion test presages the least expensive medication (mexiletine) (table 6).

## Conclusions

There are limited data available examining the use of intravenous analgesic testing. For all of these tests, there is simply not enough available evidence to make definitive conclusions regarding their predictive value. On the basis of the available evidence, this systematic review demonstrates that intravenous analgesic tests have limited overall clinical utility in selecting patients for long-term treatment with specific oral analgesic agents.

## References

1. Ram S, Kumar SK, Clark GT: Using oral medications, infusions and injections for differential diagnosis of orofacial pain. J Calif Dent Assoc 2006; 34: 645–54

2. Vickers ER, Cousins MJ: Neuropathic orofacial pain. Part 2-Diagnostic procedures, treatment guidelines and case reports. Aust Endod J 2000; 26:53–63

3. Arner S: Intravenous phentolamine test: Diagnostic and prognostic use in reflex sympathetic dystrophy. Pain 1991; 46:17–22
4. O'Gorman DA, Raja SN: Drug infusions for the diagnosis and treatment of chronic pain. Curr Pain Headache Rep 2002; 6:452–9
5. Galer BS, Miller KV, Rowbotham MC: Response to intravenous lidocaine infusion differs based on clinical diagnosis and site of nervous system injury. Neurology 1993; 43:1233–5
6. Davis KD, Treede RD, Raja SN, Meyer RA, Campbell JN: Topical application of clonidine relieves hyperalgesia in patients with sympathetically maintained pain. Pain 1991; 47:309–17
7. Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D: Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology 2004; 62:218–25
8. Galer BS, Harle J, Rowbotham MC: Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: A prospective study. J Pain Symptom Manage 1996; 12:161–7
9. Dellemijn PL, van Duijn H, Vanneste JA: Prolonged treatment with transdermal fentanyl in neuropathic pain. J Pain Symptom Manage 1998; 16:220–9
10. Dellemijn PL, Vanneste JA: Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. Lancet 1997; 349:753–8
11. Huse E, Larbig W, Flor H, Birbaumer N: The effect of opioids on phantom limb pain and cortical reorganization. Pain 2001; 90:47–55
12. Canavero S, Bonicalzi V: Intravenous subhypnotic propofol in central pain: A double-blind, placebo-controlled, crossover study. Clin Neuropharmacol 2004; 27:182–6
13. Cohen SP, Chang AS, Larkin T, Mao J: The intravenous ketamine test: A predictive response tool for oral dextromethorphan treatment in neuropathic pain. Anesth Analg 2004; 99:1753–9
14. Canavero S, Bonicalzi V: Extradural cortical stimulation for central pain. Acta Neurochir Suppl 2007; 97:27–36
15. Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Yoshimine T: Motor cortex stimulation for central and peripheral deafferentation pain. Report of eight cases. J Neurosurg 2000; 92:150–5
16. Saitoh Y, Hirano S, Kato A, Kishima H, Hirata M, Yamamoto K, Yoshimine T: Motor cortex stimulation for deafferentation pain. Neurosurg Focus 2001; 11:E1
17. Gustorff B: Intravenous opioid testing in patients with chronic non-cancer pain. Eur J Pain 2005; 9:123–5
18. Sindrup SH, Jensen TS: Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999; 83:389–400
19. Siu A, Drachtman R: Dextromethorphan: A review of *N*-methyl-D-aspartate receptor antagonist in the management of pain. CNS Drug Rev 2007; 13:96–106
20. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996; 17:1–12
21. Geurts JW, van Wijk RM, Stolker RJ, Groen GJ: Efficacy of radiofrequency procedures for the treatment of spinal pain: A systematic review of randomized clinical trials. Reg Anesth Pain Med 2001; 26:394–400
22. Calatayud J, Gonzalez A: History of the development and evolution of local anesthesia since the coca leaf. ANESTHESIOLOGY 2003; 98:1503–8
23. Bartlett EE, Hutaserani Q: Lidocaine (xylocaine) for the relief of postoperative pain. J Am Med Womens Assoc 1962; 17:809–15
24. Boas RA, Covino BG, Shahnarian A: Analgesic responses to i.v. lignocaine. Br J Anaesth 1982; 54:501–5
25. Amir R, Argoff CE, Bennett GJ, Cummins TR, Durieux ME, Gerner P, Gold MS, Porreca F, Strichartz GR: The role of sodium channels in chronic inflammatory and neuropathic pain. J Pain 2006; 7:S1–29
26. Hargus NJ, Patel MK: Voltage-gated Na+ channels in neuropathic pain. Expert Opin Investig Drugs 2007; 16:635–46
27. Black JA, Liu S, Tanaka M, Cummins TR, Waxman SG: Changes in the expression of tetrodotoxin-sensitive sodium channels within dorsal root ganglia neurons in inflammatory pain. Pain 2004; 108:237–47
28. Matzner O, Devor M: Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na+ channels. J Neurophysiol 1994; 72:349–59
29. Wall PD, Devor M: Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve injured rats. Pain 1983; 17:321–39
30. Wu G, Ringkamp M, Murinson BB, Pogatzki EM, Hartke TV, Weerahandi HM, Campbell JN, Griffin JW, Meyer RA: Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. J Neurosci 2002; 22:7746–53
31. Devor M, Seltzer Z: Pathophysiology of damaged nerves in relation to chronic pain, Textbook of Pain, 4th Edition. Edited by Wall PD, Melzack R. London, UK, Churchill Livingstone, 1999, pp 129–64
32. Dong XW, Goregoaker S, Engler H, Zhou X, Mark L, Crona J, Terry R, Hunter J, Priestley T: Small interfering RNA-mediated selective knockdown of Na(V)1.8 tetrodotoxin-resistant sodium channel reverses mechanical allodynia in neuropathic rats. Neuroscience 2007; 146:812–21
33. Nieto FR, Entrena JM, Cendan CM, Pozo ED, Vela JM, Baeyens JM: Tetrodotoxin inhibits the development and expression of neuropathic pain induced by paclitaxel in mice. Pain 2008; 137:520–31
34. Challapalli V, Tremont-Lukats IW, McNicol ED, Lau J, Carr DB: Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database Syst Rev 2005: CD003345
35. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q: The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002; 95:985–91
36. Fassoulaki A, Sarantopoulos C, Melemeni A, Hogan Q: Regional block and mexiletine: The effect on pain after cancer breast surgery. Reg Anesth Pain Med 2001; 26:223–8
37. Mao J, Chen LL: Systemic lidocaine for neuropathic pain relief. Pain 2000; 87:7–17
38. Ichimata M, Ikebe H, Yoshitake S, Hattori S, Iwasaka H, Noguchi T: Analgesic effects of flecainide on postherpetic neuralgia. Int J Clin Pharmacol Res 2001; 21:15–9
39. Lindstrom P, Lindblom U: The analgesic effect of tocainide in trigeminal neuralgia. Pain 1987; 28:45–50
40. Sakurai M, Kanazawa I: Positive symptoms in multiple sclerosis: Their treatment with sodium channel blockers, lidocaine and mexiletine. J Neurol Sci 1999; 162:162–8
41. Trentin L, Visentin M: The predictive lidocaine test in treatment of neuropathic pain (in Italian). Minerva Anestesiol 2000; 66:157–61
42. Bleakman D, Alt A, Nisenbaum ES: Glutamate receptors and pain. Semin Cell Dev Biol 2006; 17:592–604
43. Childers WE Jr, Baudy RB: N-methyl-D-aspartate antagonists and neuropathic pain: The search for relief. J Med Chem 2007; 50:2557–62
44. Raith K, Hochhaus G: Drugs used in the treatment of opioid tolerance and physical dependence: A review. Int J Clin Pharmacol Ther 2004; 42:191–203
45. Chizh BA, Headley PM: NMDA antagonists and neuropathic pain–multiple drug targets and multiple uses. Curr Pharm Des 2005; 11:2977–94
46. Laube B, Kuhse J, Betz H: Evidence for a tetrameric structure of recombinant NMDA receptors. J Neurosci 1998; 18:2954–61
47. De Kock MF, Lavand'homme PM: The clinical role of NMDA receptor antagonists for the treatment of postoperative pain. Best Pract Res Clin Anaesthesiol 2007; 21:85–98
48. McCartney CJ, Sinha A, Katz J: A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesth Analg 2004; 98:1385–400
49. Okon T: Ketamine: An introduction for the pain and palliative medicine physician. Pain Physician 2007; 10:493–500
50. Sang CN, Booher S, Gilron I, Parada S, Max MB: Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: Efficacy and dose-response trials. ANESTHESIOLOGY 2002; 96:1053–61
51. Haines DR, Gaines SP: N of 1 randomised controlled trials of oral ketamine in patients with chronic pain. Pain 1999; 83:283–7
52. Lauretti GR, Lima IC, Reis MP, Prado WA, Pereira NL: Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. ANESTHESIOLOGY 1999; 90:1528–33
53. Henriksson KG, Sorensen J: The promise of N-methyl-D-aspartate receptor antagonists in fibromyalgia. Rheum Dis Clin North Am 2002; 28:343–51
54. Klepstad P, Borchgrevink PC: Four years' treatment with ketamine and a trial of dextromethorphan in a patient with severe post-herpetic neuralgia. Acta Anaesthesiol Scand 1997; 41:422–6
55. Burton AW, Lee DH, Saab C, Chung JM: Preemptive intrathecal ketamine injection produces a long-lasting decrease in neuropathic pain behaviors in a rat model. Reg Anesth Pain Med 1999; 24:208–13
56. Davar G, Hama A, Deykin A, Vos B, Maciewicz R: MK-801 blocks the development of thermal hyperalgesia in a rat model of experimental painful neuropathy. Brain Res 1991; 553:327–30
57. Mao J, Price DD, Hayes RL, Lu J, Mayer DJ: Differential roles of NMDA and non-NMDA receptor activation in induction and maintenance of thermal hyperalgesia in rats with painful peripheral mononeuropathy. Brain Res 1992; 598: 271–8
58. Zhang GH, Yoon YW, Lee KS, Min SS, Hong SK, Park JY, Han HC: The glutamatergic N-methyl-D-aspartate and non-N-methyl-D-aspartate receptors in the joint contribute to the induction, but not maintenance, of arthritic pain in rats. Neurosci Lett 2003; 351:177–80
59. Zhang GH, Min SS, Lee KS, Back SK, Yoon SJ, Yoon YW, Kim YI, Na HS, Hong SK, Han HC: Intraarticular pretreatment with ketamine and memantine could prevent arthritic pain: Relevance to the decrease of spinal c-fos expression in rats. Anesth Analg 2004; 99:152–8
60. Cohen SP, Verdolin MH, Chang AS, Kurihara C, Morlando BJ, Mao J: The intravenous ketamine test predicts subsequent response to an oral dextromethorphan treatment regimen in fibromyalgia patients. J Pain 2006; 7:391–8
61. Cohen SP, Wang S, Chen L, Kurihara C, McKnight G, Marcuson M, Mao J: An intravenous ketamine test as a predictive response tool in opioid-exposed patients with persistent pain. J Pain Symptom Manage 2009; 37:698–708
62. Furuhashi-Yonaha A, Iida H, Asano T, Takeda T, Dohi S: Short- and long-term efficacy of oral ketamine in eight chronic-pain patients. Can J Anaesth 2002; 49:886–7
63. Blum RH: A history of opium, Society and drugs. Edited by Blum RH, San Francisco, Jossey-Bass Inc, 1969, pp 45–58
64. Janson W, Stein C: Peripheral opioid analgesia. Curr Pharm Biotechnol 2003; 4:270–4

65. Benedetti F, Vighetti S, Amanzio M, Casadio C, Oliaro A, Bergamasco B, Maggi G: Dose-response relationship of opioids in nociceptive and neuropathic postoperative pain. Pain 1998; 74:205–11

66. Cherny NI, Thaler HT, Friedlander-Klar H, Lapin J, Foley KM, Houde R, Portenoy RK: Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: A combined analysis of controlled, single-dose studies. Neurology 1994; 44:857–61

67. Mercadante S: Opioid responsiveness in patients with advanced head and neck cancer. Support Care Cancer 1998; 6:482–5

68. Ballantyne JC, Mao J: Opioid therapy for chronic pain. N Engl J Med 2003; 349:1943–53

69. Chou R, Clark E, Helfand M: Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: A systematic review. J Pain Symptom Manage 2003; 26:1026–48

70. Eisenberg E, McNicol ED, Carr DB: Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: Systematic review and meta-analysis of randomized controlled trials. JAMA 2005; 293:3043–52

71. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E: Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. CMAJ 2006; 174:1589–94

72. Kalso E, Edwards JE, Moore RA, McQuay HJ: Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. Pain 2004; 112:372–80

73. Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, Fiellin DA: Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann Intern Med 2007; 146:116–27

74. Noble M, Tregear SJ, Treadwell JR, Schoelles K: Long-term opioid therapy for chronic noncancer pain: A systematic review and meta-analysis of efficacy and safety. J Pain Symptom Manage 2008; 35:214–28

75. Cohen SP, Raja SN: The middle way: A practical approach to prescribing opioids for chronic pain. Nat Clin Pract Neurol 2006; 2:580–1

76. Katz NP, Sherburne S, Beach M, Rose RJ, Vielguth J, Bradley J, Fanciullo GJ: Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg 2003; 97:1097–102

77. Kirsh KL, Whitcomb LA, Donaghy K, Passik SD: Abuse and addiction issues in medically ill patients with pain: attempts at clarification of terms and empirical study. Clin J Pain 2002; 18:S52–60

78. Miotto K, Compton P, Ling W, Conolly M: Diagnosing addictive disease in chronic pain patients. Psychosomatics 1996; 37:223–35

79. Dellemijn P: Are opioids effective in relieving neuropathic pain? Pain 1999; 80:453–62

80. Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D: Effects of IV morphine in central pain: A randomized placebo-controlled study. Neurology 2002; 58:554–63

81. Chaturvedi A, Dash HH: Sympathetic blockade for the relief of chronic pain. J Indian Med Assoc 2001; 99:698–703

82. Gamal G, Helaly M, Labib YM: Superior hypogastric block: Transdiscal *versus* classic posterior approach in pelvic cancer pain. Clin J Pain 2006; 22: 544–7

83. Longmire DR: An electrophysiological approach to the evaluation of regional sympathetic dysfunction: A proposed classification. Pain Physician 2006; 9:69–82

84. Mailis A, Furlan A: Sympathectomy for neuropathic pain. Cochrane Database Syst Rev 2003:CD002918

85. Martinez-Lavin M: Is fibromyalgia a generalized reflex sympathetic dystrophy? Clin Exp Rheumatol 2001; 19:1–3

86. Yan BM, Myers RP: Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol 2007; 102:430–8

87. Liu X, Chung K, Chung JM: Ectopic discharges and adrenergic sensitivity of sensory neurons after spinal nerve injury. Brain Res 1999; 849:244–7

88. Shyu BC, Danielsen N, Andersson SA, Dahlin LB: Effects of sympathetic stimulation on C-fibre response after peripheral nerve compression: An experimental study in the rabbit common peroneal nerve. Acta Physiol Scand 1990; 140:237–43

89. Lavand'homme PM, Ma W, De Kock M, Eisenach JC: Perineural alpha (2A)-adrenoceptor activation inhibits spinal cord neuroplasticity and tactile allodynia after nerve injury. ANESTHESIOLOGY 2002; 97:972–80

90. Bossut DF, Shea VK, Perl ER: Sympathectomy induces adrenergic excitability of cutaneous C-fiber nociceptors. J Neurophysiol 1996; 75:514–7

91. Drummond PD, Skipworth S, Finch PM: Alpha 1-adrenoceptors in normal and hyperalgesic human skin. Clin Sci (Lond) 1996; 91:73–7

92. Raja SN, Davis KD, Campbell JN: The adrenergic pharmacology of sympathetically-maintained pain. J Reconstr Microsurg 1992; 8:63–9

93. Devor M, Janig W, Michaelis M: Modulation of activity in dorsal root ganglion neurons by sympathetic activation in nerve-injured rats. J Neurophysiol 1994; 71:38–47

94. McLachlan EM, Janig W, Devor M, Michaelis M: Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. Nature 1993; 363: 543–6

95. Wasner G, Heckmann K, Maier C, Baron R: Vascular abnormalities in acute reflex sympathetic dystrophy (CRPS I): Complete inhibition of sympathetic nerve activity with recovery. Arch Neurol 1999; 56:613–20

96. Feigl GC, Rosmarin W, Stelzl A, Weninger B, Likar R: Comparison of different injectate volumes for stellate ganglion block: an anatomic and radiologic study. Reg Anesth Pain Med 2007; 32:203–8

97. Medrik-Goldberg T, Lifschitz D, Pud D, Adler R, Eisenberg E: Intravenous lidocaine, amantadine, and placebo in the treatment of sciatica: A double-blind, randomized, controlled study. Reg Anesth Pain Med 1999; 24:534–40

98. Wu CL, Tella P, Staats PS, Vaslav R, Kazim DA, Wesselmann U, Raja SN: Analgesic effects of intravenous lidocaine and morphine on postamputation pain: A randomized double-blind, active placebo-controlled, crossover trial. ANESTHESIOLOGY 2002; 96:841–8

99. Raja SN, Treede RD, Davis KD, Campbell JN: Systemic alpha-adrenergic blockade with phentolamine: A diagnostic test for sympathetically maintained pain. ANESTHESIOLOGY 1991; 74:691–8

100. Dellemijn PL, Fields HL, Allen RR, McKay WR, Rowbotham MC: The interpretation of pain relief and sensory changes following sympathetic blockade. Brain 1994; 117:1475–87

101. Wehnert Y, Muller B, Larsen B, Kohn D: Sympathetically maintained pain (SMP): Phentolamine test *versus* sympathetic nerve blockade (in German). Comparison of two diagnostic methods. Orthopade 2002; 31:1076–83

102. Byas-Smith MG, Max MB, Muir J, Kingman A: Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage 'enriched enrollment' design. Pain 1995; 60:267–74

103. Finnerup NB, Otto M, Jensen TS, Sindrup SH: An evidence-based algorithm for the treatment of neuropathic pain. Med Gen Med 2007; 9:36

104. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH: Algorithm for neuropathic pain treatment: An evidence based proposal. Pain 2005; 118:289–305

105. Woolf CJ: Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004; 140:441–51

106. Woolf CJ, Max MB: Mechanism-based pain diagnosis: Issues for analgesic drug development. ANESTHESIOLOGY 2001; 95:241–9

107. Benedetti F: Placebo analgesia. Neurol Sci 2006; 27 (Suppl 2):S100–2

108. Koshi EB, Short CA: Placebo theory and its implications for research and clinical practice: A review of the recent literature. Pain Pract 2007; 7:4–20

109. Dworkin RH, Katz J, Gitlin MJ: Placebo response in clinical trials of depression and its implications for research on chronic neuropathic pain. Neurology 2005; 65:S7–19

110. Gliedman LH, Gantt WH, Teitelbaum HA: Some implications of conditional reflex studies for placebo research. Am J Psychiatry 1957; 113:1103–7

111. Goldstein AP: Participant expectancies in psychotherapy. Psychiatry 1962; 25:72–9

112. Wasan AD, Kaptchuk TJ, Davar G, Jamison RN: The association between psychopathology and placebo analgesia in patients with discogenic low back pain. Pain Med 2006; 7:217–28

113. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M: The placebo effect and its determinants in osteoarthritis: Meta-analysis of randomised controlled trials. Ann Rheum Dis 2008; 67:1716–23

114. Milburn A, Reiter RC, Rhomberg AT: Multidisciplinary approach to chronic pelvic pain. Obstet Gynecol Clin North Am 1993; 20:643–61

115. Cohen SP, Argoff CE, Carragee EJ: Management of low back pain. BMJ 2008; 337:a2718

116. Littlejohn GO, Walker J: A realistic approach to managing patients with fibromyalgia. Curr Rheumatol Rep 2002; 4:286–92

117. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J: Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003; 106:337–45

118. Ferrante FM, Paggioli J, Cherukuri S, Arthur GR: The analgesic response to intravenous lidocaine in the treatment of neuropathic pain. Anesth Analg 1996; 82:91–7

119. Kastrup J, Petersen P, Dejgard A, Angelo HR, Hilsted J: Intravenous lidocaine infusion–A new treatment of chronic painful diabetic neuropathy? Pain 1987; 28:69–75

120. Galer BS, Sheldon E, Patel N, Codding C, Burch F, Gammaitoni AR: Topical lidocaine patch 5% may target a novel underlying pain mechanism in osteoarthritis. Curr Med Res Opin 2004; 20:1455–8

121. Puig S, Sorkin LS: Formalin-evoked activity in identified primary afferent fibers: Systemic lidocaine suppresses phase-2 activity. Pain 1996; 64:345–55

122. Legroux-Crespel E, Sassolas B, Guillet G, Kupfer I, Dupre D, Misery L: Treatment of familial erythermalgia with the association of lidocaine and mexiletine (in French). Ann Dermatol Venereol 2003; 130:429–33

123. Ohara S, Hayashi R, Momoi H, Miki J, Yanagisawa N: Mexiletine in the treatment of spasmodic torticollis. Mov Disord 1998; 13:934–40

124. Chaplan SR, Bach FW, Shafer SL, Yaksh TL: Prolonged alleviation of tactile allodynia by intravenous lidocaine in neuropathic rats. ANESTHESIOLOGY 1995; 83:775–85

125. Araujo MC, Sinnott CJ, Strichartz GR: Multiple phases of relief from experimental mechanical allodynia by systemic lidocaine: Responses to early and late infusions. Pain 2003; 103:21–9

126. Sinnott CJ, Garfield JM, Strichartz GR: Differential efficacy of intravenous lidocaine in alleviating ipsilateral *versus* contralateral neuropathic pain in the rat. Pain 1999; 80:521–31

127. Carroll I: Intravenous lidocaine for neuropathic pain: Diagnostic utility and therapeutic efficacy. Curr Pain Headache Rep 2007; 11:20–4

128. Tremont-Lukats IW, Challapalli V, McNicol ED, Lau J, Carr DB: Systemic administration of local anesthetics to relieve neuropathic pain: A systematic review and meta-analysis. Anesth Analg 2005; 101:1738–49

129. Rathmell JP, Ballantyne JC: Local anesthetics for the treatment of neuropathic pain: On the limits of meta-analysis. Anesth Analg 2005; 101:1736–7

130. Carroll IR, Kaplan KM, Mackey SC: Mexiletine therapy for chronic pain: Survival analysis identifies factors predicting clinical success. J Pain Symptom Manage 2008; 35:321–6

131. Moore RA, McQuay HJ: Prevalence of opioid adverse events in chronic non-malignant pain: Systematic review of randomised trials of oral opioids. Arthritis Res Ther 2005; 7:R1046–51

132. Jensen MK, Thomsen AB, Hojsted J: 10-year follow-up of chronic non-malignant pain patients: Opioid use, health related quality of life and health care utilization. Eur J Pain 2006; 10:423–33

133. Maier C, Schaub C, Willweber-Strumpf A, Zenz M: Long-term efficiency of opioid medication in patients with chronic non-cancer-associated pain. Results of a survey 5 years after onset of medical treatment (in German). Schmerz 2005; 19:410–7

134. Cohen SP, Dragovich A: Intrathecal analgesia. Anesthesiol Clin 2007; 25:863–82

135. Mystakidou K, Parpa E, Tsilika E, Mavromati A, Smyrniotis V, Georgaki S, Vlahos L: Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. J Pain 2003; 4:298–306

136. Ackerman WE, Zhang JM: Efficacy of stellate ganglion blockade for the management of type 1 complex regional pain syndrome. South Med J 2006; 99:1084–8

137. Price DD, Long S, Wilsey B, Rafii A: Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. Clin J Pain 1998; 14:216–26

138. Di Filippo A, Natale V, Del Po F, Ciapetti M, Bressan F, Falchi S: Skin temperature during sympathetic block: A clinical comparison of bupivacaine 0.5% and ropivacaine 0.5% or 0.75%. Anaesth Intensive Care 2006; 34:334–7

139. Dick AM, Gabbott DA, Hardy PA: Plasma concentrations of bupivacaine following single needle lumbar sympathectomy using two volumes of 0.25% bupivacaine plain solution. Anaesthesia 1996; 51:750–1

140. Meno A, Arita H, Hanaoka K: Preliminary report: The efficacy of clonidine hydrochloride ointment for postherpetic neuralgia (in Japanese). Masui 2001; 50:160–3

141. Wolff M, Heugel P, Hempelmann G, Scholz A, Muhling J, Olschewski A: Clonidine reduces the excitability of spinal dorsal horn neurones. Br J Anaesth 2007; 98:353–61

142. Tryba M, Gehling M: Clonidine–A potent analgesic adjuvant. Curr Opin Anaesthesiol 2002; 15:511–7

143. Bredfeldt RC, Sutherland JE, Kruse JE: Efficacy of transdermal clonidine for headache prophylaxis and reduction of narcotic use in migraine patients. A randomized crossover trial. J Fam Pract 1989; 29:153–6

144. D'Andrea G, Perini F, Granella F, Cananzi A, Sergi A: Efficacy of transdermal clonidine in short-term treatment of cluster headache: A pilot study. Cephalalgia 1995; 15:430–3

145. Zeigler D, Lynch SA, Muir J, Benjamin J, Max MB: Transdermal clonidine *versus* placebo in painful diabetic neuropathy. Pain 1992; 48:403–8

146. Edmondson EA, Simpson RK Jr, Stubler DK, Beric A: Systemic lidocaine therapy for poststroke pain. South Med J 1993; 86:1093–6

147. Phillips WJ, Tollefson B, Johnson A, Abell T, Lerant A: Relief of acute pain in chronic idiopathic gastroparesis with intravenous phentolamine. Ann Pharmacother 2006; 40:2032–6

## Appendix

Evaluation Criteria for Included Studies (one point for each):

1. Were data prospectively recorded?
2. Was the study appropriately randomized?
3. Was the infusion test blinded?
4. Was the definitive treatment phase double-blinded?
5. Did all patients who received an intravenous infusion test proceed to definitive treatment?
6. Were counterinterventions avoided?
7. Did the study size exceed 20 patients?
8. Was there a clear description of inclusion and exclusion criteria?
9. Was there a clear description of the infusion test?
10. Was there a clear description of definitive treatment parameters?