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 infusions tests: lidocaine, ketamine, opioid, and phenolamine. The studies evaluating all intravenous infusions 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 phenolamine 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 infusions 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, the 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 infusions tests have been associated with few responders (a high number-need-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 patient 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, 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 infusions tests include elucidating pain mechanisms that may guide development of future treatments, establishing target doses 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 patient 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, 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 infusions 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 infusions 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
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 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. The analgesic effect of systemic lidocaine was first reported in 1961, when Bartlett and Hutaserani used an intravenous infusion to treat post-operative 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. 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 subunit and one or two smaller ancillary subunits. Among the 10 known channel isoforms, 9 have been cloned and are functionally expressed. 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients and Conditions</th>
<th>Quality Score, 0–10 Scale</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Results and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attal,7 2004</td>
<td>22 pts with postherpetic neuralgia or nerve trauma</td>
<td>9</td>
<td>DB, PC with open-label f/u</td>
<td>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)</td>
<td>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</td>
</tr>
<tr>
<td>Legroux-Crespel,122 2003</td>
<td>4 pts with erythromelalgia</td>
<td>3</td>
<td>Observational</td>
<td>100–200 mg of lido IV infused followed by 200–600 mg/d mex</td>
<td>Paroxysmal flares improved in all pts by 3rd day and persisted for 2 yrs; evaluated combined therapy, not correlation</td>
</tr>
</tbody>
</table>
| Trentin,41 2000 | 183 pts with central and peripheral neuropathic pain            | 4                         | Retrospective           | 4 mg/kg lido IV followed by various sodium channel 1 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%)
| 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           | 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 torticolis                                 | 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,145 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; 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 NC 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 |


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.51 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 μM, 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 responders 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.

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 μg/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.41 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.42 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-hydroxy-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-aspartate (NMDA) glutamate receptor.

Activation of the NMDA receptor (NMDA-R) enhances sustained neuronal depolarization, thereby contributing to increased excitatory transmission along afferent 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
Table 2. Studies Examining the Value of IV Ketamine Testing in Predicting Response to Subsequent Treatment in Patients with Chronic Pain

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients and Conditions</th>
<th>Quality Score, 0–10 Scale</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Results and Comments</th>
</tr>
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<tbody>
<tr>
<td>Cohen,13 2004</td>
<td>25 pts with neuropathic pain</td>
<td>7</td>
<td>Retrospective</td>
<td>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</td>
<td>The optimal cutoff 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</td>
</tr>
<tr>
<td>Cohen,60 2006</td>
<td>34 pts with fibromyalgia</td>
<td>7</td>
<td>Observational</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Cohen,61 2008</td>
<td>56 opioid-tolerant chronic pain pts</td>
<td>7</td>
<td>Observational</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td>Furuhashi-Yonah,62 2002</td>
<td>8 with chronic neuropathic pain</td>
<td>5</td>
<td>Randomized, PC</td>
<td>Pts who responded to an IV ket infusion (dose not noted) received either placebo or 0.5 mg/kg every 6 h oral ket</td>
<td>All pts obtained &gt; 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 (&gt; 9 mo) benefit with treatment</td>
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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.\(^65\) 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,\(^65\) but more recent studies have demonstrated efficacy for all types of pain conditions, albeit in different dose ranges.\(^{58,70}\) 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.\(^71\) 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.\(^73\) 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.\(^8\) 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 fentanyl (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...
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 sympathetic maintained pain (SMP). There are several mechanisms by which denervations 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 α-1 adrenoreceptors on primary afferent nociceptors \(^89\)\(^{,90} \) and hyperalgesic skin of complex regional pain syndrome patients \(^91\) central sensitization rendering A-β 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. \(^96\)\(^{,97} \) 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

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<th>Quality Score (0–10 Scale)</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Results and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dellemijn,(^9)(^{,10} ) 1997–8</td>
<td>48 pts with neuropathic pain who took part in a previous DB, PC crossover trial</td>
<td>7</td>
<td>Open-label prospective study in pts who participated in a DB, PC trial comparing IV fentanyl, diazepam, and saline</td>
<td>53 pts received either IV fentanyl (5 µg · kg(^{-1} ) · h(^{-1} )) and diazepam (0.2 µg · kg(^{-1} ) · 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 µg/h) for 12 weeks</td>
<td>In the DB, PC study, fentanyl (66% relief) &gt; diazepam (23%) &gt; saline (12%); a significant correlation was found between pain reduction during the IV fentanyl infusion and transdermal treatment phase</td>
</tr>
<tr>
<td>Huse,(^11) 2001</td>
<td>12 pts with phantom limb pain</td>
<td>8</td>
<td>DB, PC, crossover</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Attal,(^6)(^0) 2002</td>
<td>16 pts with central pain</td>
<td>8</td>
<td>DB, PC, crossover with open-label follow-up</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Agarwal,(^<em>) 2005(^</em>)</td>
<td>26 pts with postamputation pain</td>
<td>7</td>
<td>DB, PC, 2-phase crossover study</td>
<td>Double-blind IV morphine (0.05 mg/kg), lidocaine, or placebo infusion on 3 consecutive days, followed by DB crossover study comparing oral agents</td>
<td>No significant correlation (r = 0.24) between IV and oral MSO4 response; among 13 IV MSO4 responders, 8 responded to oral MSO4; among 10 IV nonresponders, only 1 had a negative response to oral MSO4</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Conditions</th>
<th>Quality Score (0–10 Scale)</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Results and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillips,147</td>
<td>37-year-old woman with idiopathic gastroparesis and abdominal pain</td>
<td>4</td>
<td>Case report</td>
<td>Pt received &gt; 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</td>
<td>Pain scores and long-term follow-up not noted on clonidine</td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Byas-Smith,102</td>
<td>41 pts with diabetic neuropathy</td>
<td>7</td>
<td>Phase 1: DB, PC, 3-phase crossover; Phase II: DB, PC, 3-phase crossover, followed by a blinded IV phentolamine test in CR</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davis,6 1991</td>
<td>6 subjects with neuropathic pain and hyperalgesia</td>
<td>5</td>
<td>Open-label prospective study</td>
<td>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</td>
<td>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</td>
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<tr>
<td>Amer,3 1991</td>
<td>104 patients with reflex sympathetic dystrophy, including 54 children</td>
<td>6</td>
<td>Observational study</td>
<td>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</td>
<td>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</td>
</tr>
</tbody>
</table>

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

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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 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 guanethidine 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

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* 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.

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 the 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,\textsuperscript{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).

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

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>IV lidocaine (n = 6)\textsuperscript{*}</td>
<td>100% (89–100%) (20–100%)</td>
<td>72% (47–90%) (29–100%)</td>
<td>55% (20–83%) (17–100%)</td>
<td>68% (40–85%) (12–100%)</td>
<td>2b</td>
<td>B</td>
<td>$15#</td>
</tr>
<tr>
<td>IV ketamine (n = 3)\textsuperscript{†}</td>
<td>76%</td>
<td>78%</td>
<td>67%</td>
<td>85%</td>
<td>3a</td>
<td>B–C</td>
<td>$50**</td>
</tr>
<tr>
<td>IV opioids (n = 4)\textsuperscript{‡}</td>
<td>66% (49–91%) (50–100%)</td>
<td>72% (44–75%) (17–77%)</td>
<td>52% (40–60%) (33–62%)</td>
<td>90% (49–96%) (10–100%)</td>
<td>Evidence conflicting</td>
<td>D</td>
<td>$23‡‡</td>
</tr>
<tr>
<td>IV phentolamine (n = 3)\textsuperscript{§}</td>
<td>68% (0–100%) (0–100%)</td>
<td>70% (40–100%) (40–100%)</td>
<td>62.5% (25–100%) (25–100%)</td>
<td>75.5% (51–100%) (51–100%)</td>
<td>Evidence lacking</td>
<td>D</td>
<td>$151‡‡</td>
</tr>
</tbody>
</table>

* 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 only 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.\textsuperscript{11} § Positive response to IV phentolamine test and clonidine or guanethidine 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 clonidine patches. ** 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).\textsuperscript{18,105,104} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{112} In several of the studies analyzed, patients were selected for definitive therapy on the sole basis of their response to intravenous testing.\textsuperscript{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.\textsuperscript{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.\textsuperscript{114–116} Although several evaluated studies did exclude patients with serious psychiatric illness,\textsuperscript{7,11,13,60,61,80} only two evaluated psychological indices as an outcome measure.\textsuperscript{9,11} Psychological wellbeing is widely acknowledged to be one of the core outcome domains of chronic pain clinical trials\textsuperscript{117};
therefore, future investigations should endeavor to include emotional outcome measures.

**Intravenous 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.\(^{122,125}\) Although animal studies have reported long-term benefit after systemic lidocaine,\(^{124–126}\) the evidence for sustained pain relief in humans is 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 mexiletine, the long-term effectiveness of mexiletine 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 mexiletine 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 mexiletine.\(^{130}\)

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 1yr 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 (0.1mg/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.\(^{13}\) 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.\(^{7,132–134}\) 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 case 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, 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).

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 blocks, a minimal temperature rise of at least 1°C has been used to document a sympathectomy, although much greater temperature changes are often noted in cool extremities. Second, whereas Davis et al. 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. Even among the four responders in the former study, 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. Finally, in only one of the three studies were patients selected on the basis of presence of autonomic dysfunction. 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. 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. 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, 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; 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


36. Anesthesiology, V 111, No 2, Aug 2009


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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


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?