An Intravenous Ketamine Test as a Predictive Response Tool in Opioid-Exposed Patients with Persistent Pain

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Abstract

Chronic pain patients who are treated with opioid therapy represent a significant challenge to medical professionals. When pain recurs in the face of a previously effective opioid regimen, treatment options include dose escalation, opioid rotation, drug holidays, and the addition of adjuvants. Some experts advocate the use of N-methyl-D-aspartate receptor (NMDA-R) antagonists to combat tolerance. Recently, the use of an intravenous (i.v.) ketamine infusion to predict the response to a dextromethorphan (DX) treatment trial has been described. In this study, 56 opioid-exposed patients with recurrent pain were treated with a low-dose (0.1 mg/kg) i.v. ketamine test followed by a DX treatment course. Using previously designated cutoff values for a positive response to ketamine (67% or more pain relief) and DX (50% or more pain relief), the sensitivity, specificity, positive predictive value, and negative predictive value for an i.v. ketamine infusion to predict subsequent response to DX treatment were 72%, 68%, 52%, and 85%, respectively. The observed agreement between analgesic responses was 78%, indicating a highly significant correlation ($r = 0.54, P = 0.0001$). Subgroup classification revealed no significant differences in the response to either ketamine or DX treatment based on pain classification (i.e., nociceptive, neuropathic, or mixed) or placebo response. In contrast, a weaker correlation between ketamine and DX response was found in subjects requiring high-dose rather than low-dose opioid therapy. A significant correlation also was noted between the development of side effects for the two NMDA-R antagonists. Based on these results, we conclude that an i.v. ketamine test may be a valuable tool in predicting subsequent response to DX treatment in opioid-exposed patients with persistent pain.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Introduction

The use of intravenous (i.v.) infusion tests represents a burgeoning area of pain management.\(^1\,^2\) Originally used in an attempt to characterize the mechanisms behind chronic pain states,\(^3\,^4\) the use of receptor-specific analgesic drug infusions has experienced a recent resurgence as a prognostic tool for chronic pain treatment.\(^5\,^6\) In addition to the i.v. phentolamine test,\(^3\) clinicians have infused opioids,\(^7\,^8\) barbiturates,\(^9\) propofol,\(^10\) ketamine,\(^11\) lidocaine,\(^12\,13\) and placebo\(^8\,^9\,^11\) in elaborate attempts to predict outcome.

Recently, Cohen et al.\(^11\,14\) described the use of an i.v. ketamine test to predict response to an oral dextromethorphan (DX) treatment regimen in patients with neuropathic pain and fibromyalgia. In both studies, a receiver’s operating characteristic (ROC) curve determined the optimal cutoff to an i.v. ketamine infusion to be an identical two-thirds or more pain relief. Combining data from these studies yielded an overall sensitivity of 79% and specificity of 89%.

One criticism that can be leveled against these studies is that neither involved nociceptive pain or targeted patients on high-dose opioids. Whereas fibromyalgia is well recognized as a distinct clinical entity, its classification as a syndrome rather than a disease presupposes multifactorial etiologies.\(^15\) Furthermore, both experimental pain models and clinical data indicate that central mechanisms are likely to play a pivotal role in the disorder.\(^16\,\,19\) Although preclinical and clinical studies strongly support the efficacy of N-methyl-D-aspartate receptor (NMDA-R) antagonists in neuropathic pain, their benefit for nociceptive pain is weak and inconsistent.\(^20\,21\)

The evidence supporting NMDA-R antagonists in patients on high-dose opioid therapy is conflicting. Preclinical studies conducted in rodents demonstrated that the NMDA-R antagonist DX potentiates opioid analgesia\(^22\,23\) and attenuates tolerance.\(^24\,25\) Yet, although early clinical studies seemed to confirm a synergistic effect between DX and opioids,\(^26\,28\) later controlled studies failed to demonstrate any added benefit for combination pharmacotherapy.\(^29\) The purpose of this study is to evaluate the ability of an i.v. ketamine infusion to predict response to a DX treatment regimen in opioid-exposed patients with persistent pain, as stratified by pain classification (i.e., neuropathic or nociceptive) and opioid dose.

Patients and Methods

Permission to conduct this study was granted by the Walter Reed Army Medical Center (WRAMC) Department of Clinical Investigation, and all patients who gave their informed consent for the trials. Inclusion criteria were Department of Defense beneficiaries 18 years or more in age, opioid dose of 60 mg or more oral morphine equivalents per day, and clinical opioid tolerance defined by significant worsening pain in the context of a well-maintained opioid regimen and no evidence of worsening pathology. Exclusion criteria were any change in opioid or other analgesic medications less than 30 days before the scheduled procedure, an inability to understand English or adequately respond to the relevant questions, and an unstable medical (e.g., uncontrolled hypertension) or psychiatric (e.g., untreated depression) condition that might preclude an optimal treatment response. For complete details regarding the rationale for performing the i.v. ketamine test at military treatment facilities, readers are referred to our previous work.\(^11\,14\) Data were garnered from a prospectively maintained database set up for i.v. infusion trials. All procedures were performed at WRAMC.
between 2002 and 2007 as part of standard clinical treatment. A post hoc power analysis conducted using the SPSS program indicated that a sample size of 56 had a 97% chance of detecting a Pearson correlation coefficient of 0.5 (effect size) when controlling for a Type I error at $\alpha = 0.05$.

Procedure

Before the infusion test, all subjects completed 0–10 numeric rating scales (NRS) for pain. After inserting a small-gauge i.v. catheter, an infusion of normal saline was begun, which was followed shortly thereafter by the bolus administration of 0.25 mg of midazolam. Approximately five minutes later, 0.1 mg/kg of ketamine was administered over seven minutes. Immediately preceding the ketamine infusion, and five minutes after its completion, 0–10 verbal rating scale pain scores were obtained, representing post-midazolam (i.e., placebo response) and post-ketamine scores, respectively. As per previously published guidelines,12,14 all subjects were blinded to the contents and timing of injections.

After the i.v. ketamine infusion, computerized prescriptions for DX were entered into the pharmacy database on all patients irrespective of their response, and filled pending approval from the Anesthesia and Pharmacy Services. The starting dose was 30 mg per os two (BID) or three times per day (TID), contingent on weight, titrating up to a target dose of 1 mg/kg per os TID as tolerated. In 39 patients, prescriptions were filled within seven days. In 10 patients, prescriptions were filled between eight and 14 days after the test. Eight patients filled their prescriptions after 14 days, all because of supply difficulties. Before starting the DX treatment regimen, subjects provided a verbal rating score through telephone or e-mail. Response to DX was obtained using an NRS in all patients during their first follow-up six to eight weeks after commencing treatment. During the study period, no changes in analgesic medication regimens were made.

Data Collection

The following demographic and clinical data were recorded for analysis: age, sex, duration of pain, opioid dose, pain classification (e.g., nociceptive, neuropathic, or mixed) pre-infusion NRS score, post-midazolam pain score, post-ketamine pain score, pre-DX pain score, post-DX treatment pain score, and side effects to both medications. Based on identical findings from two previous studies,11,14 whereby an ROC curve determined two-thirds or more pain relief after ketamine infusion to be the optimal cutoff for predicting response to DX treatment, 67% or more and 50% or more pain relief were pre-defined to indicate a positive response to the ketamine test and DX therapy, respectively. After treatment, all subjects were placed into one of four categories: positive response to both ketamine and DX; negative response to ketamine and DX; positive response to ketamine and negative response to DX; and negative response to ketamine and positive response to DX.

Statistical Analysis

Statistical analyses were performed using the software SPSS. Categorical data are reported both by number of patients and percentage. Continuous data are reported as mean and standard deviation unless otherwise indicated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are based on 67% or more pain relief with the i.v. ketamine test and 50% or more pain relief with DX, which were pre-determined by ROC curves to be the optimal cutoff values in previous studies.11,14 Correlations between the response to ketamine and DX treatment were calculated using the Pearson correlation coefficient. Paired $t$-tests were used to compare the effects of a named medication before and after its administration in all subgroup analyses. Differences were considered to be statistically significant at the level of $P < 0.05$.

Results

The mean age for the 56 study subjects was 47.6 years (standard deviation [SD] 15.3, range 19–80). There were 29 females and 27 males, with all subjects exhibiting clinical signs of opioid tolerance. All subjects completed the ketamine infusion, followed by an oral DX treatment regimen. Excluding one subject on a morphine equivalent dose (MED) of 16,000 mg, the mean opioid dose was 178.5 mg (SD 157.9, range 60–780).
Among the four categories of responses to the ketamine/DX regimens, 13 patients experienced a positive response to both ketamine and DX, 26 patients exhibited negative responses to both medications, 12 patients obtained a positive response to ketamine but a negative response to DX, and five patients responded negatively to ketamine but positively to DX. There were no differences in gender distribution or duration of pain symptoms, nor were there statistically significant differences in opioid doses among the four response categories (Table 1).

For those subjects responding positively to both ketamine and DX, the mean baseline pain score was 6.3 (SD 1.6), which declined to 0.7 (SD 1.0; \( P < 0.001 \)) after the i.v. ketamine test. The average pain score was comparably decreased from a pre-DX mean of 6.5 (SD 1.8) to 1.8 (SD 1.4; \( P < 0.001 \)) after DX treatment. Among the 46% (\( n = 26 \)) of subjects who responded negatively to both drugs, the mean pre- and post-ketamine scores were 6.4 (SD 2.2) and 4.9 (SD 1.9; \( P < 0.001 \)), respectively. After DX treatment, the average pain score only slightly diminished from 6.3 (SD 2.2) to 5.7 (SD 1.8; \( P < 0.05 \)). Only five patients who responded negatively to the ketamine infusion experienced significant pain relief after the DX treatment regimen, indicating that a potentially beneficial treatment would have been withheld from less than 10% of participants had a positive response to ketamine been used as the sole DX treatment criterion.

Overall, a strong correlation was found between pain reduction after the ketamine infusion and oral DX treatment (Fig. 1, \( R = 0.54, P = 0.0001 \)), as determined by Pearson’s correlation coefficient. Those subjects who responded positively to the i.v. ketamine test demonstrated a robust tendency to respond with similar intermediate-term pain relief after

### Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>(+)Ket/(+D)X (( n = 13 ))</th>
<th>(-)Ket/(-D)X (( n = 26 ))</th>
<th>(+)Ket/(-D)X (( n = 12 ))</th>
<th>(-)Ket/(+D)X (( n = 5 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>45.7 (13.4)</td>
<td>48.0 (18.0)</td>
<td>47.1 (14.1)</td>
<td>52.4 (10.5)</td>
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<tr>
<td>Gender</td>
<td>9M, 4F</td>
<td>9M, 17F</td>
<td>6M, 6F</td>
<td>3M, 2F</td>
</tr>
<tr>
<td>Duration of symptoms in years, mean (SD)</td>
<td>4.7 (2.9)</td>
<td>5.5 (4.5)</td>
<td>4.8 (5.6)</td>
<td>4.9 (4.0)</td>
</tr>
<tr>
<td>Pain classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nociceptive (( n = 22 ))</td>
<td>4 (18%)</td>
<td>10 (46%)</td>
<td>8 (36%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neuropathic (( n = 23 ))</td>
<td>3 (13%)</td>
<td>13 (57%)</td>
<td>3 (13%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Mixed (( n = 11 ))</td>
<td>6 (55%)</td>
<td>3 (27%)</td>
<td>1 (9%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Opioid dose in MED, mean (SD)*</td>
<td>173.9 (149.1)</td>
<td>152.5 (144.7)</td>
<td>196.6 (189.5)</td>
<td>282.0 (166.5)</td>
</tr>
<tr>
<td>DX dose in mg, mean (SD)</td>
<td>233.1 (91.8)</td>
<td>191.5 (58.8)</td>
<td>225.0 (76.2)</td>
<td>222.0 (76.2)</td>
</tr>
<tr>
<td>Pre-infusion NRS score, mean (SD)</td>
<td>6.3 (1.6)</td>
<td>6.4 (2.2)</td>
<td>6.2 (2.2)</td>
<td>7.3 (1.9)</td>
</tr>
<tr>
<td>Post-midazolam VRS score, mean (SD)</td>
<td>5.0 (2.2)</td>
<td>6.3 (2.1)</td>
<td>5.3 (2.2)</td>
<td>6.8 (1.6)</td>
</tr>
<tr>
<td>Post-ketamine VRS score, mean (SD)</td>
<td>0.7 (1.0)</td>
<td>4.9 (1.9)</td>
<td>0.5 (0.8)</td>
<td>4.9 (1.6)</td>
</tr>
<tr>
<td>Pre-DX VRS score, mean (SD)</td>
<td>6.5 (1.8)</td>
<td>6.3 (2.2)</td>
<td>6.3 (2.1)</td>
<td>6.8 (1.3)</td>
</tr>
<tr>
<td>Post-DX NRS score, mean (SD)</td>
<td>1.8 (1.4)</td>
<td>5.7 (1.8)</td>
<td>5.0 (1.4)</td>
<td>2.9 (0.9)</td>
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<tr>
<td>Side effects with ketamine</td>
<td>9 (69%)</td>
<td>14 (56%)</td>
<td>6 (46%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Side effects with DX</td>
<td>6 (46%)</td>
<td>7 (28%)</td>
<td>5 (39%)</td>
<td>4 (80%)</td>
</tr>
</tbody>
</table>

VRS, verbal rating scale; NRS, numerical rating scale.

*Excludes one patient on 16,000 MED.

Fig. 1. Scatter graph demonstrating a significant correlation between the response to the i.v. ketamine test and a subsequent dextromethorphan treatment regimen. The curved lines represent 95% confidence intervals. Pearson correlation coefficient = 0.54, \( P < 0.001 \).
subsequent DX treatment, whereas a negative response to ketamine was likely to precede a negative response to DX (Fig. 2). Of 56 subjects included in this analysis, 39 subjects (70%) followed this pattern of consistent responses to ketamine and DX. The sensitivity, specificity, PPV, and NPV for the overall group were 72%, 68%, 52%, and 84%, respectively.

**Influence of Pain Classification on Ketamine/DX Treatment Response**

In order to determine whether the type of pain influenced the response to therapy, subjects were categorized into the following three groups based on pain characterization (Table 2). The first group, nociceptive pain \((n = 22)\), included pain conditions, such as rheumatoid or osteoarthritis \((n = 6)\), mechanical low back pain \((n = 4)\), and war-related trauma \((n = 4)\). The second group, neuropathic pain \((n = 23)\), included diagnoses peripheral neuropathy \((n = 7)\), complex regional pain syndrome \((n = 5)\), and radiculopathy \((n = 3)\). The third category was mixed pain \((n = 11)\), which comprised, predominantly, patients carrying a diagnosis of failed back surgery syndrome \((n = 8)\). Subgroup analysis indicated that neither pain condition (results not shown) nor the type of pain experienced significantly influenced the analgesic response to ketamine, DX, or the correlation between the two (Table 2).

For example, the mean NRS pain score was reduced from a pre-ketamine baseline of 6.5 (SD 2.4) to 4.0 (SD 2.8; \(P < 0.001\)) after the ketamine infusion in the neuropathic pain group. Before and after DX treatment, the mean pain scores were 6.6 (SD 2.1) and 4.8 (SD 2.1; \(P < 0.005\)), respectively. Similar results were obtained for the nociceptive and mixed pain groups (Table 2, Fig. 3).

There was a strong correlation between the response to ketamine and oral DX treatment for those subjects in the nociceptive (Table 2, \(R = 0.62; P = 0.002\)) and neuropathic pain group (Table 2, \(R = 0.48; P = 0.02\)), as determined by Pearson’s correlation coefficient analysis. In the mixed pain group, the correlation between the response to the ketamine infusion and oral DX treatment did not reach statistical significance owing to the smaller sample size (Table 2, \(R = 0.42; P = 0.17\)). The sensitivity, specificity, PPV, and NPV for the nociceptive pain group were 100%, 56%, 33%, and 100%, respectively; for the neuropathic pain group, these values were 43%, 81%, 33%, and 100%, respectively; for the neuropathic pain group, these values were 43%, 81%, 50%, and 77%, respectively. In the mixed pain group, the sensitivity, specificity, PPV, and NPV were 86%, 75%, 86%, and 75%, respectively.

**Influence of Opioid Dose on Ketamine/DX Treatment Response**

To examine whether daily opioid consumption influenced the response to NMDA-R antagonism, subjects were classified into high- and low-dose opioid groups. The high-dose group included 31 subjects whose daily MED was 120 mg or more, whereas the low-dose group comprised 25 subjects taking less than 120 mg MED. Analysis by opioid dose stratification indicated that the amount of opioid analgesics a patient was taking slightly altered the ketamine/DX treatment response (Table 3). For the high-dose opioid group, the mean pain score declined from a pre-ketamine baseline of 6.2 (SD 2.1) to 2.9 (SD 2.6; \(P < 0.001\)) after the i.v. ketamine test, and from 6.1 (SD 1.8) to 4.5 (SD 2.4; \(P < 0.001\)) after DX treatment. Among patients taking low-dose opioids, the average pain score decreased from a baseline of 6.7 (SD 2.0) to 3.1 (SD 2.9, \(P < 0.001\)) after ketamine administration, and from a mean pre-DX score of 6.8 (SD 2.2) to 4.3 (SD 2.0, \(P < 0.001\)) after the oral DX treatment regimen. As determined by Pearson’s

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**Fig. 2.** Linear graph demonstrating the change in pain scores for ketamine responders and nonresponders during study course.

**Fig. 3.**
correlation coefficient analysis, a strong correlation was noted between the response to the ketamine infusion and oral DX treatment for those subjects in the low-dose opioid group (Table 3, $R = 0.66; P < 0.0001$). In contrast, there was a weaker correlation between the response to the ketamine infusion and subsequent oral DX treatment for those subjects requiring higher-dose opioid therapy (Table 3, $R = 0.34; P = 0.095$). The sensitivity, specificity, PPV, and NPV for the low-dose opioid group were 80%, 71%, 57%, and 88%, respectively; in the high-dose opioid group, these values were 63%, 65%, 46%, and 79%, respectively.

### Influence of a Placebo Effect on the Ketamine/DX Response

As per previous guidelines, a placebo response was considered as any decrease in pain score after the administration of DX. In the low-dose opioid group, the placebo response was 39%, 56%, and 40% for ketamine, midazolam, and ketamine, respectively. In the high-dose opioid group, the placebo response was 39%, 40%, and 40% for ketamine, midazolam, and ketamine, respectively. The overall placebo response was 40% for both low and high-dose opioid groups.

### Table 3

**Demographic and Clinical Data Stratified by Opioid Dose**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Opioid Dose ≤ 120</th>
<th>Opioid Dose &gt; 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean (SD)</td>
<td>6.2 (2.1)</td>
<td>6.7 (2.0)</td>
</tr>
<tr>
<td>Duration of symptoms (yr), mean</td>
<td>5.4 (2.1)</td>
<td>6.3 (2.0)</td>
</tr>
<tr>
<td>Opioid dose (MED), mean (SD)</td>
<td>2.9 (2.6)</td>
<td>3.1 (2.9)</td>
</tr>
<tr>
<td>DX dose (mg), mean (SD)</td>
<td>6.1 (1.8)</td>
<td>6.8 (2.2)</td>
</tr>
<tr>
<td>Pre-DX NRS score, mean (SD)</td>
<td>4.5 (2.4)</td>
<td>4.3 (2.0)</td>
</tr>
<tr>
<td>Side effects with ketamine</td>
<td>19 (61%)</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Side effects with DX</td>
<td>12 (39%)</td>
<td>10 (40%)</td>
</tr>
</tbody>
</table>

Pearson correlation coefficient refers to correlation between response to ketamine and DX.

*Excludes one patient on 16,000 MED.*
a subclinical dose of midazolam (0.25 mg), which was given empirically to reduce the likelihood of untoward effects from the i.v. ketamine test. Among the 56 study participants, 22 (39%) experienced a one or more point decrease in baseline pain, and were hence classified as placebo responders. Subgroup data analysis indicated that: 1) midazolam did not significantly affect the overall pain scores irrespective of pain classification (Table 2) or opioid dose (Table 3); and 2) there were no significant differences in the response to ketamine administration or DX treatment between placebo responders (n = 22) and nonresponders (n = 34; Fig. 4).

Side Effect Profiles
Seventy-three percent (n = 41) of patients reported side effects during either the i.v. ketamine test or subsequent DX treatment. These patients included 19 who experienced adverse effects only with ketamine, eight with only DX, and 14 with both drugs. Among patients who experienced ketamine-related side effects, the three most frequently reported were dizziness, anxiety, and euphoria. Among 22 patients who experienced side effects with DX, the two most common ones were nausea and sedation. There were no statistically significant differences in side effect profiles between patients suffering from different pain classifications (Table 2), based on opioid dose (Table 3), or as a function of response to either ketamine or DX treatment (Table 1). The PPV for ketamine side effects to presage DX adverse effects was 64%. The NPV for an absence of ketamine adverse effects to foretell tolerability of DX treatment was 65%.

Discussion
The rationale behind an i.v. infusion test is that an accurate trial can improve medical care by reducing risks and conserving resources. There are several scenarios wherein this becomes relevant. The first is when an i.v. infusion is used as a prognostic tool for a treatment that carries considerable risk, such as implantable devices or when initiating opioid therapy. Although response to an i.v. infusion may not identify patients predisposed to addiction or who fail opioid therapy secondary to long-term adverse effects, it can potentially reduce these occurrences by screening out those patients likely to fail treatment. A second situation in which infusion tests can be valuable is when the definitive treatment provides considerable relief to a select group of patients, requires a long titration period, or is associated with substantial costs—all of which apply to DX therapy. In controlled studies evaluating the benefit of DX for chronic pain, approximately half demonstrate benefit, which highlights the need for improved selection criteria (Table 4). Oral ketamine has previously been used to treat chronic pain, but can be difficult to obtain, expensive to compound, possesses myriad untoward side effects, and the evidence for efficacy is weak and conflicting. Whereas a favorable side effect profile is one advantage of DX, the long titration period and lack of insurance coverage for over-the-counter medications can pose significant obstacles to effective treatment, which bolster the case for developing an accurate predictive tool. Other potential benefits of i.v. infusion tests, including ketamine, comprise elucidating pain mechanisms that may guide future treatment, establishing target doses for drugs with a wide therapeutic index, and predicting side effects in those patients inclined to experience them.
The primary goals of this study were to examine whether a correlation exists between the response to a low-dose i.v. ketamine infusion and a subsequent oral DX treatment regimen in opioid-exposed subjects with persistent pain secondary to a variety of chronic pain conditions, and whether an i.v. ketamine test can be used as a screening tool for treatment with DX in this population. The data demonstrate that there is a statistically significant correlation between the analgesic responses to i.v. ketamine and oral DX in opioid-exposed subjects irrespective of pain classification or opioid dose. These findings are consistent with previous studies using a similar experimental paradigm in non-opioid-tolerant patients. The present results provide new information on the effectiveness of using a ketamine infusion as a possible screening test to select which patients are likely to respond to oral DX treatment.

An important observation that supports the use of an i.v. ketamine test in subjects on opioid therapy is that, although about one-fourth of study subjects enrolled in this study demonstrated positive responses to both ketamine and DX, nearly half the subjects failed to respond to either medication, indicating that only a subset of patients receiving opioid therapy have a clinical pain condition mediated through an NMDA-R mechanism. Thus, the use of a quick, reliable screening tool might

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of Patients</th>
<th>Condition</th>
<th>Treatment/DX Dose</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dudgeon et al., 2007</td>
<td>65</td>
<td>Cancer</td>
<td>Morphine + DX (240–480 mg/d) vs. morphine + placebo</td>
<td>14 days</td>
<td>Nonsignificant effect favoring DX</td>
</tr>
<tr>
<td>Panitch et al., 2006</td>
<td>150</td>
<td>Multiple sclerosis</td>
<td>Quinidine (60 mg/d) + DX (60 mg/d) vs. placebo</td>
<td>12 weeks</td>
<td>&gt; Placebo for pain</td>
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<tr>
<td>Galer et al., 2005</td>
<td>three studies, 828 pts</td>
<td>Nonmalignant, non-neuropathic, chronic pain</td>
<td>Morphine + DX in 1:1 ratio (107 pts had 2:1 ratio) vs. Morphine alone at dose range of 45–360 mg/d</td>
<td>90 days</td>
<td>No difference</td>
</tr>
<tr>
<td>Carlsson et al., 2004</td>
<td>15</td>
<td>Traumatic, neuropathic pain</td>
<td>270 mg/d</td>
<td>Four hours after treatment</td>
<td>&gt; Placebo</td>
</tr>
<tr>
<td>Ben Abraham et al., 2003</td>
<td>10</td>
<td>Phantom pain</td>
<td>120–180/d; 270 mg/d in open-label phase</td>
<td>10 days per treatment phase; 90 days for open-label phase</td>
<td>&gt; Placebo for both doses. 120mg = 180mg/d dose</td>
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<td>Sang et al., 2002</td>
<td>44</td>
<td>Diabetic neuropathy and postherpetic neuralgia</td>
<td>Median dose 400 mg/d (up to 960 mg/d)</td>
<td>Nine weeks</td>
<td>Diabetic neuropathy: DX &gt; memantine &gt; placebo; Postherpetic neuralgia: no difference between groups No difference</td>
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<td>Heiskanen et al., 2002</td>
<td>20</td>
<td>Neuropathic pain</td>
<td>100 mg DX or placebo followed by 15 mg i.v. morphine</td>
<td>Two hours</td>
<td>No difference</td>
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<td>Gilron et al., 2000</td>
<td>19</td>
<td>Facial pain</td>
<td>Mean doses of 178–357 mg/d, up to 640 mg/d</td>
<td>Six weeks</td>
<td>No difference</td>
</tr>
<tr>
<td>Nelson et al., 1997</td>
<td>32</td>
<td>Diabetic neuropathy and postherpetic neuralgia</td>
<td>Mean doses of 381–439 mg/d</td>
<td>Six weeks</td>
<td>Diabetic neuropathy: DX &gt; placebo Postherpetic neuralgia: no difference between groups No difference</td>
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<td>McQuay et al., 1994</td>
<td>21</td>
<td>Neuropathic and central pain</td>
<td>40–80 mg/d</td>
<td>10 days</td>
<td>No difference</td>
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</tbody>
</table>
prevent unnecessary treatment, and conserve time and financial resources. This finding is consistent with our previous study in patients with fibromyalgia. Interestingly, the response (or lack thereof) to ketamine and DX was not dependent on the type of pain condition, suggesting that the clinical classification of neuropathic and nociceptive pain may be difficult, and in many cases, unnecessary. The administration of subclinical midazolam before the infusion test provided neither significant pain relief nor influenced the response to ketamine, suggesting that the response to the i.v. ketamine test was unlikely attributable to a placebo effect.

Several issues need to be considered in the interpretation of our results. First, quantitative sensory testing (QST) was not used in this study because QST is time-consuming and not readily available in most pain centers. Although QST may be helpful in differentiating allodynia from hyperalgesia, most subjects in our study did not present with either of these symptoms. Second, the numeric pain score was used to assess treatment response because this scoring system is easy to administer and the most commonly used pain instrument. The Brief Pain and Beck's Depression Inventories were not included, because the main focus of this study was to provide an overall assessment of the predictive value of the i.v. ketamine test on a subsequent DX regimen. Although these indices can provide important screening and outcome information in clinical trials, their use in this context might be construed as redundant. Third, the subject size was relatively small in this study, although a post hoc power analysis indicated the feasibility of drawing statistically meaningful conclusions. A larger sample size in future investigations might improve data interpretation and conceivably lead to different conclusions. Fourth, whereas this study can be regarded as single-blinded, as no patient knew the sequence of i.v. injections (midazolam or ketamine), this design would not necessarily have precluded expectation bias from influencing the response to DX treatment. However, this effect is to some extent clinically mitigated by the relatively low percentage of patients in the negative ketamine/positive DX treatment group, and the absence of any predictive value of placebo response for definitive treatment with DX.

It should be emphasized that the current study was not intended to evaluate whether a ketamine infusion or DX treatment is a remedy for opioid tolerance, because it was not designed to determine whether pain reduction (or lack thereof) after either ketamine or DX treatment was caused by the reversal of clinical opioid tolerance, pain relief, or a combination of the two. It is possible that a longer duration of treatment with ketamine or DX, or a higher dose of these medications, might be required to reverse opioid tolerance, as suggested by preclinical studies using NMDA-R antagonists. In contrast, NMDA-R antagonists have been shown to reverse neuropathic pain behaviors in preclinical studies even after a single administration, suggesting that a positive response to ketamine and DX (i.e., reduction of pain scores) might be the result of the effect of these drugs on pain.

This study was not designed to detect clinical efficacy. A clinical trial whose purpose is to evaluate the effectiveness of DX in opioid-exposed patients with persistent pain would ideally include a control group and longer follow-up period. Alternative explanations for the beneficial effects observed in our patients include expectation bias (i.e., a patient who positively responded to ketamine might have high expectations for subsequent therapy), placebo effect, the sedative properties of DX, and alterations in opioid bioavailability. Although no association was found between the response to placebo and ketamine or DX in the current study, previous studies showed a positive correlation between pain relief after a subclinical dose of midazolam and analgesia after a DX treatment regimen.

Some experts might question our reluctance to frame this patient population as “opioid tolerant.” Opioid tolerance is a complex clinical condition rife with semantic ambiguity and misapplication. In humans, opioid tolerance manifests as diminished analgesic effect and/or the need for dose escalation to maintain steady levels of symptom control. Multiple factors may contribute to apparent opioid tolerance, including pharmacological tolerance (pharmacokinetiand/or pharmacodynamic), disease progression, and opioid-induced hyperalgesia. Although subjects in this study exhibited no overt evidence of disease progression that could explain their reduced
response to opioids, their disease work-up was not standardized. Furthermore, effectively distinguishing between opioid-induced nociceptor sensitization and receptor desensitization study might require a drug holiday, which was not performed. Hence, because the cause of apparent opioid tolerance in these subjects was not definitively determined, we referred to these subjects as opioid-exposed patients with persistent pain.

Despite the conflicting reports of the effects NMDA-R antagonism have on chronic pain and opioid tolerance, the current data suggest that a subset of opioid-exposed patients with persistent pain may benefit from treatment with clinically available NMDA-R antagonists. More research is needed to determine the long-term effects of DX treatment in chronic pain patients on high-dose opioid therapy, and to identify those patients most suitable for treatment.

References


