Review Article

NMDA Receptor Antagonists for the Treatment of Neuropathic Pain

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This study is part of TREND (Trauma RElated Neuronal Dysfunction), a knowledge consortium that integrates research on Complex Regional Pain Syndrome type 1 (CRPS 1). This project is supported by a Dutch Government grant (BSIK03016).

Abstract

Objective. The N-methyl-D-Aspartate (NMDA) receptor has been proposed as a primary target for the treatment of neuropathic pain. The aim of the present study was to perform a meta-analysis evaluating the effects of (individual) NMDA receptor antagonists on neuropathic pain, and the response (sensitivity) of individual neuropathic pain disorders to NMDA receptor antagonist therapy.

Design. PubMed (including MEDLINE), EMBASE and CENTRAL were searched up to October 26, 2009 for randomized placebo controlled trials (RCTs) on neuropathic pain. The methodological quality of the included trials was independently assessed by two authors using the Delphi list. Fixed or random effects model were used to calculate the summary effect size using Hedges’ g.

Setting. NA.

Patients. The patients used for the study were neuropathic pain patients.

Interventions. The interventions used were NMDA receptor antagonists.

Outcome measurements. The outcome of measurements was the reduction of spontaneous pain.

Results. Twenty-eight studies were included, meeting the inclusion criteria. Summary effect sizes were calculated for subgroups of studies evaluating ketamine IV in complex regional pain syndrome (CRPS), oral memantine in postherpetic neuralgia and, respectively, ketamine IV, and oral memantine in postamputation pain. Treatment with ketamine significantly reduced pain in postamputation pain (pooled summary effect size: −1.18 [confidence interval (CI) 95% −1.98, −0.37], P = 0.004). No significant effect on pain reduction could be established for ketamine IV in CRPS (−0.65 [CI 95% −1.47, 0.16], P = 0.11) oral memantine in postherpetic neuralgia (0.03 [CI 95% −0.51, 0.56], P = 0.92) and for oral memantine in postamputation pain (0.38 [CI 95% −0.21, 0.98], P = 0.21).

Conclusions. Based on this systematic review, no conclusions can yet be made about the efficacy of NMDA receptor antagonists on neuropathic pain. Additional RCTs in homogenous groups of pain patients are needed to explore the therapeutic potential of NMDA receptor antagonists in neuropathic pain.

Key Words. Meta-Analysis; NMDA Receptor Antagonists; Neuropathic Pain

Introduction

Neuropathic pain is pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [1]. Neuropathic pain is manifested in disorders of various etiologies such as post-herpetic neuralgia, diabetic neuropathy, and complex regional pain syndrome...
Several therapies have been developed for the treatment of neuropathic pain; however, these methods are not equally effective for all neuropathic pain patients [6]. The N-methyl-D-Aspartate (NMDA) receptor has been proposed as a primary target for the treatment of neuropathic pain. Evidence suggests that the NMDA receptor within the dorsal horn plays an important role in both inflammation and nerve injury-induced central sensitization [7]. Prolonged pain stimuli of high intensity induce a cascade of events which activate the NMDA receptor. Activation of the NMDA receptor is associated with abnormalities in the sensory (peripheral and central) system, resulting in neuronal excitation and abnormal pain manifestations (spontaneous pain, allodynia, hyperalgesia) [8–10]. Blocking of these receptors by antagonists may possibly impede or reverse the pain pathology, leading to a reduction of pain [11].

The effects of NMDA receptor antagonists on neuropathic pain patients of various etiologies have been investigated in clinical trials in which positive as well as negative outcomes on pain relief were found. Considering the present ambiguity with respect to the general efficacy of NMDA receptor antagonists, a research synthesis of literature is warranted. To date, no meta-analysis has been performed with respect to the efficacy of NMDA receptor antagonists for treatment of features of neuropathic pain.

Therefore, the aim of the present study was to perform a meta-analysis evaluating the effects of NMDA receptor antagonists on neuropathic pain.

Furthermore, subgroup analyses will be performed in assessing the effects of individual NMDA receptor antagonists on neuropathic pain and their response on individual neuropathic pain disorders, testing the hypothesis that NMDA receptor antagonists are effective in the treatment of neuropathic pain.

Methods

Inclusion Criteria

Studies were sought that examined the effect of NMDA receptor antagonists on spontaneous pain in acute and chronic neuropathic pain [1] patients of all ages. Studies had to be blinded, randomized, placebo controlled, and the outcome pain had to be recorded on a numerical rating scale.

Results

Quantitative Analysis

The studies were analyzed using the effect size Hedges’ g (standardized mean difference) [15,16], which is calculated by the difference between the experiment and control treatment at the end of the treatment period, divided by the pooled standard deviation (SD) (see Appendix). A heterogeneity test statistics I² [17,18] was determined to assess whether a fixed or random effects model was appropriate to calculate the summary effect size using Hedges’ g. A fixed effect model was used when the
The pooled effects of studies could be considered homogeneous ($I^2$ statistics below 25%) [18].

The difference in pain relief between experimental and placebo conditions as measured on a numerical rating scale was taken as the primary outcome measure. In case data for quantitative analysis were not present in the article, written permission for additional data was requested from the authors of these articles. If no additional information was obtained from the author, the effect size was estimated from significance levels, assuming conservative values (e.g., $P = 0.5$ if not significant; $P = 0.05$ if significant). For each study, a weighting factor ($W_i$) was estimated, assigning larger weights to effect sizes from studies with larger samples and, thus, smaller variances. For studies evaluating different interventions or different doses within the same study, the interventions were regarded as independent treatments and therefore effect sizes were calculated separately for each intervention compared with placebo.

The summary effect size was then established by averaging the individual effect sizes. For each individual effect size and for the summary effect size, a 95% confidence interval was obtained. The summary effect size was only calculated for similar interventions in patients with the same pain conditions. Furthermore, the summary effect size will only be reported for studies with a quality assessment score of more than 50% [13]. Cohen [19] has provided reference points to serve as guide in the interpretation of effect sizes: 0.20 for “small” effects, 0.50 for “moderate” effects and 0.80 for “large” effects. For all outcome variables, the significance level was set at 0.05.

**Results**

**Quality of Studies**

Twenty-eight studies were included meeting the inclusion criteria (Figure 1) [20–46]. One included study was written by MS [45], accordingly, the methodological quality of this study was independently assessed by SC and RP. The level of agreement between the authors, with respect to the quality assessment, as measured with the kappa was good (mean kappa for the 11 items: 0.93 SD 0.03). The studies were of good quality (median quality score 8 [interquartile range 7–9]) (Table 1), except for the studies of Furuhashi-Yonaha [46] and Schiffito [41] in which a quality score of 2 and 3, respectively, were found.

**Description of Studies**

Twenty-three studies were of a crossover design and in five studies, a parallel design was used (Table 1). In two studies, active placebo (lorazepam) were used [27,32]. The interventions were evaluated in 572 neuropathic pain patients of various etiologies (complex regional pain syndrome $n = 126$; postherpetic neuralgia $n = 103$; amputation pain $n = 75$; diabetic neuropathy $n = 55$; peripheral neuropathy other than diabetic $n = 19$; HIV pain $n = 45$; sciatica $n = 30$; pain caused by operation $n = 23$; caused by traumas other than operation $n = 32$; peripheral nerve injury $n = 24$; verified nerve injury $n = 10$; posttraumatic neuralgia $n = 11$; trigeminal neuropathy $n = 10$; anesthesia dolorosa $n = 4$; idiopathic trigeminal neuralgia $n = 2$; visceral pain $n = 2$; spinal cord injury $n = 1$). Pain was measured with numerical rating scale (0–10 or 0–100) scores except for the study of Sang et al. which used the Gracely

![Figure 1](image-url) Flow chart of study selection.
<table>
<thead>
<tr>
<th>Authors</th>
<th>QS</th>
<th>N</th>
<th>Patients</th>
<th>Interventions</th>
<th>Appl</th>
<th>Design</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Individual effect size (inverse variance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max et al. 1995</td>
<td>7</td>
<td>7</td>
<td>Posttraumatic pain and allodynia</td>
<td>Ketamine: 2 h, 0.75 mg/kg/h</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain after 2 hours</td>
<td>Ketamine significantly reduced background pain, ( p = 0.01 )</td>
<td>-0.88 [-1.98, 0.22]</td>
</tr>
<tr>
<td>Felsby et al. 1995a</td>
<td>8</td>
<td>10</td>
<td>Chronic neuropathic pain (after amputation ((n = 3)), after operation ((n = 5)), after radiation ((n = 2)))</td>
<td>Ketamine: 10 min, 0.2 mg/kg and 50 min, 0.3 mg/kg/h</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain after 15 min after infusion</td>
<td>Ketamine significantly reduced pain intensity, ( p = 0.006 )</td>
<td>-0.42 [-1.41, 0.45]</td>
</tr>
<tr>
<td>Felsby et al. 1995b</td>
<td>8</td>
<td>10</td>
<td>Chronic neuropathic pain (after amputation ((n = 3)), after operation ((n = 5)), after radiation ((n = 2)))</td>
<td>MgCl₂: 10 min, 0.16 mmol/kg and 50 min 0.16 mmol/kg/h</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain after 15 min after infusion</td>
<td>MgCl₂ significantly reduced pain intensity, ( p = 0.084 )</td>
<td>-0.29 [-1.22, 0.64]</td>
</tr>
<tr>
<td>Nickolajsen et al. 1996</td>
<td>8</td>
<td>11</td>
<td>Post amputation stump and phantom limb pain</td>
<td>Ketamine: bolus 0.1 mg/kg/5 min and 7 µg/kg/min for 40 min</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain after infusion</td>
<td>Ketamine significantly reduced stump and phantom pain, ( p &lt; 0.05^* )</td>
<td>-0.89 [-1.78, 0.01]</td>
</tr>
<tr>
<td>Eisenberg et al. 1998</td>
<td>10</td>
<td>20</td>
<td>Postherptic neuralgia</td>
<td>Memantine: wk 1:10 mg/d, wk 2/5: 20 mg/d</td>
<td>Oral</td>
<td>Parallel</td>
<td>VAS (0–10) pain after 5 weeks</td>
<td>No statistically significant difference in reduction of pain</td>
<td>0.23 [-0.65, 1.11]</td>
</tr>
<tr>
<td>Pud et al. 1998</td>
<td>7</td>
<td>13</td>
<td>Surgical neuropathic pain in cancer patients</td>
<td>Amantadine: 200 mg in 3 hours</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain after 3 h infusions</td>
<td>Amantadine significantly reduced pain, ( p = 0.0001 )</td>
<td>-1.46 [-2.32, -0.60]</td>
</tr>
<tr>
<td>Medrik-Goldberg et al. 1999</td>
<td>9</td>
<td>30</td>
<td>Sciatica</td>
<td>Amantadine: 2.5 mg/kg in 2 hours</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain after 180 min</td>
<td>No statistically significant difference in reduction of spontaneous pain</td>
<td>0.04 [-0.47, 0.55]</td>
</tr>
<tr>
<td>Galer et al. 2000a</td>
<td>9</td>
<td>22</td>
<td>Peripheral neuropathic pain (postherptic neuralgia ((n = 13)), diabetic polyneuropathy ((n = 1)), peripheral neuropathy other than diabetic ((n = 8)))</td>
<td>Riluzole: 100 mg/d for 2 weeks</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 2 weeks</td>
<td>No statistically significant difference in alleviating peripheral neuropathic pain, ( p &gt; 0.10 )</td>
<td>0.26 [-0.34, 0.86]</td>
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<tr>
<td>Authors</td>
<td>QS</td>
<td>N</td>
<td>Patients</td>
<td>Interventions</td>
<td>Appl</td>
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<td>Primary outcome</td>
<td>Results</td>
<td>Individual effect size (inverse variance)</td>
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<tr>
<td>Galer et al. 2000b</td>
<td>9</td>
<td>21</td>
<td>Peripheral neuropathic pain (postherptic neuralgia (n = 9), diabetic polyneuropathy (n = 1), peripheral neuropathy other than diabetic (n = 11))</td>
<td>Riluzole: 200 mg/d for 2 weeks</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 2 weeks</td>
<td>No statistically significant difference in alleviating peripheral neuropathic pain, ( p &gt; 0.10 )</td>
<td>(-0.07 [-0.68, 0.54])</td>
</tr>
<tr>
<td>Gilron et al. 2000</td>
<td>8</td>
<td>16</td>
<td>Facial neuralgias (possible trigeminal neuropathy (n = 10), anaesthesia dolorosa (n = 4), idiopathic trigeminal neuralgia (n = 2))</td>
<td>Dextromethorphan: 120 mg/d, titrated to max 20 mg/d for 6 weeks</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS overall daily pain after 6 weeks</td>
<td>No statistically significant difference in reducing pain, ( p = 0.81 )</td>
<td>(0.05 [-0.64, 0.74])</td>
</tr>
<tr>
<td>Nickolajsen et al. 2000</td>
<td>7</td>
<td>15</td>
<td>Neuropathic pain after amputation (n = 12) or operation (n = 3)</td>
<td>Memantine: wk 1: 5 mg/d, wk 2: 10 mg/d, wk 3: 15 mg/d, wk 4/5: 20 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS (0–10) pain during wk 4/5</td>
<td>No significant difference in reducing spontaneous pain</td>
<td>(-0.41 [-1.14, 0.32])</td>
</tr>
<tr>
<td>Leung et al. 2001</td>
<td>7</td>
<td>12</td>
<td>Neuropathic pain (postherptic neuralgia (n = 4), CRPS (n = 7), spinal cord injury (n = 1))</td>
<td>Ketamine: target plasma levels of 50, 100 and 150 ng/ml</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS at 3 plasma levels</td>
<td>No significant reduction in spontaneous pain*</td>
<td>(0.28 [-0.52, 1.08])</td>
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<td>Abraham et al. 2002a</td>
<td>8</td>
<td>3</td>
<td>Phantom pain in cancer amputees</td>
<td>Dextromethorphan: 1 wk 120 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 1 week</td>
<td>Dextromethorphan significantly reduced post amputation phantom limb pain, ( p &lt; 0.05^* )</td>
<td>(-2.27 [-4.42, -0.12])</td>
</tr>
<tr>
<td>Abraham et al. 2002b</td>
<td>8</td>
<td>3</td>
<td>Phantom pain in cancer amputees</td>
<td>Dextromethorphan: 1 wk 180 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 1 week</td>
<td>Dextromethorphan significantly reduced post amputation phantom limb pain, ( p &lt; 0.05^* )</td>
<td>(-2.27 [-4.42, -0.12])</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Disease/Condition</td>
<td>Treatment</td>
<td>Route</td>
<td>Outcome</td>
<td>Data</td>
<td>Notes</td>
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<td>Brill et al. 2002</td>
<td>2002</td>
<td>Postherptic neuralgia</td>
<td>MgSO4: 30 mg/kg MgSO4 in 30 min IV</td>
<td>Crossover</td>
<td>VAS pain after 30 minutes</td>
<td>MgSO4 significantly reduced postherptic neuralgia pain, ( p = 0.016^* )</td>
<td>(-1.50 [-2.68, -0.36])</td>
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<td>Furuhashi-Yonaha et al. 2002</td>
<td>2002</td>
<td>CRPS (n = 4), visceral pain (n = 2), postherptic neuralgia (n = 1), phantom limb pain (n = 1)</td>
<td>Ketamine: 0.5 mg/kg every six hours for a week Oral</td>
<td>Crossover</td>
<td>VAS pain after 1 week</td>
<td>Oral ketamine significantly reduced severity of the pain, ( p &lt; 0.05 )</td>
<td>(-1.57 [-2.68, -0.44])</td>
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<tr>
<td>Sang et al. 2002a</td>
<td>2002</td>
<td>Diabetic neuropathy</td>
<td>Dextromethorphan: 7 wk titration until max tolerated doses and 2 wk maintenance, median doses 400 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>Gracely Box Scale during last week of treatment period</td>
<td>No significant difference in reducing pain</td>
<td>(-0.41 [-1.05, 0.23])</td>
<td></td>
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<tr>
<td>Sang et al. 2002b</td>
<td>2002</td>
<td>Postherptic neuralgia</td>
<td>Dextromethorphan: 7 wk titration until max tolerated doses and 2 wk maintenance, median doses 400 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>Gracely Box Scale during last week of treatment period</td>
<td>No significant difference in reducing pain</td>
<td>(-0.03 [-0.70, 0.64])</td>
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<tr>
<td>Sang et al. 2002c</td>
<td>2002</td>
<td>Diabetic neuropathy</td>
<td>Memantine: 7 wk titration until max tolerated doses and 2 wk maintenance, median doses 55 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>Gracely Box Scale during last week of treatment period</td>
<td>No significant difference in reducing pain</td>
<td>(-0.04 [-0.68, 0.60])</td>
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<tr>
<td>Sang et al. 2002d</td>
<td>2002</td>
<td>Postherptic neuralgia</td>
<td>Memantine: 7 wk titration until max tolerated doses and 2 wk maintenance, median doses 55 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>Gracely Box Scale during last week of treatment period</td>
<td>No significant difference in reducing pain</td>
<td>0.08 [-0.75, 0.59]</td>
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<td>Wallace et al. 2002</td>
<td>2002</td>
<td>Neuropathic pain (postherptic neuralgia (n = 26), peripheral nerve injury (n = 21), CRPS (n = 9), diabetic neuropathy (n = 6))</td>
<td>Glycine antagonist GV196771: 2 weeks 300 mg/d</td>
<td>Oral</td>
<td>Parallel</td>
<td>VAS pain at the end of 2 week treatment</td>
<td>No significant difference in reducing spontaneous pain, ( p = 0.513^* )</td>
<td>0.11 [-0.39, 0.61]</td>
<td></td>
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<tr>
<td>Abraham et al. 2003a</td>
<td>2003</td>
<td>Phantom pain in cancer (n = 8) and non cancer (n = 2) amputees</td>
<td>Dextromethorphan: 10 days 120 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 10 days</td>
<td>All patients reported a &gt;50% decrease in pain intensity after treatment</td>
<td>Not estimable**</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
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<td>Abraham et al. 2003b</td>
<td>6</td>
<td>10</td>
<td>Phantom pain in cancer (n = 8) and non cancer (n = 2) amputees</td>
<td>Dextromethorphan: 10 days 180 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 10 days</td>
<td>All patients reported a &gt;50% decrease in pain intensity after treatment</td>
<td>Not estimable**</td>
</tr>
<tr>
<td>Amin et al. 2003</td>
<td>8</td>
<td>17</td>
<td>Diabetic peripheral neuropathy</td>
<td>Amantadine: 1 × 200 mg in 500 ml 0.9% NaCl</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain after 1 week</td>
<td>Amantadine significantly reduced pain intensity p = 0.003</td>
<td>−0.98 [−1.71, −0.25]</td>
</tr>
<tr>
<td>Jorum et al. 2003</td>
<td>7</td>
<td>12</td>
<td>Post traumatic neuralgia (n = 11) and postherptic neuralgia (n = 1)</td>
<td>Ketamine: bolus 60 µg/kg and 6 µg/kg for 20 min</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain after infusion</td>
<td>Ketamine significantly reduced spontaneous pain p = 0.015*</td>
<td>−1.08 [−1.94, −0.22]</td>
</tr>
<tr>
<td>Maier et al. 2003</td>
<td>11</td>
<td>16</td>
<td>Chronic phantom limb pain after amputation of arm or leg</td>
<td>Memantine: week 1 titration 30 mg/d; 5 mg/d + added 5 mg daily, w2+3: 30 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 3 weeks</td>
<td>No significant difference in reducing phantom limb pain</td>
<td>0.24 [−0.46, 0.94]</td>
</tr>
<tr>
<td>Carlsson et al. 2004</td>
<td>7</td>
<td>13</td>
<td>Neuropathic pain of traumatic origin</td>
<td>Dextromethorphan: 1× 270 mg</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 0–4 hours</td>
<td>Dextromethorphan significantly reduced pain, p &lt; 0.05</td>
<td>−0.81 [−1.61, −0.01]</td>
</tr>
<tr>
<td>Wiech et al. 2004</td>
<td>8</td>
<td>8</td>
<td>Chronic phantom limb pain</td>
<td>Memantine: wk 1: 10 mg/d, wk 2: 20 mg/d, wk 3/4: 30 mg/d</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 4 weeks treatment</td>
<td>No significant difference in reducing intensity of chronic limb pain, p = 0.16*</td>
<td>0.74 [−0.27, 1.05]</td>
</tr>
<tr>
<td>Gottrup et al. 2006</td>
<td>8</td>
<td>19</td>
<td>Verified nerve injury pain</td>
<td>Ketamine: bolus 0.1 mg/kg in 10 min and 0.007 mg/kg/min in 20 min</td>
<td>IV</td>
<td>Crossover</td>
<td>VAS pain during infusion</td>
<td>Ketamine significantly reduced spontaneous pain, p &lt; 0.01</td>
<td>−0.35 [−0.99, 0.29]</td>
</tr>
<tr>
<td>Schifitto et al. 2006</td>
<td>3</td>
<td>45</td>
<td>HIV associated sensory neuropathy</td>
<td>Memantine: wk 1: 10 mg/d + added weekly for 4 wk 10 mg/d, wk 4/16: 40 mg/d</td>
<td>Oral</td>
<td>Parallel</td>
<td>VAS pain after 16 weeks</td>
<td>No significant difference in reducing HIV associated sensory neuropathy, p = 0.87*</td>
<td>0.05 [−0.54, 0.64]</td>
</tr>
<tr>
<td>Forst et al. 2007a</td>
<td>10</td>
<td>12</td>
<td>Neuropathic pain (postherptic pain (n = 3), posttraumatic injury (n = 6), CRPS (n = 3))</td>
<td>Novel glutamate antagonist CNS 5161 HCl: single dose of 125 µg</td>
<td>Oral</td>
<td>Crossover</td>
<td>VAS pain after 12 hours</td>
<td>No significant difference in reducing pain</td>
<td>0.16 [−0.64, 0.96]</td>
</tr>
<tr>
<td>Study</td>
<td>PAS Cases</td>
<td>CRPS Cases</td>
<td>Participants</td>
<td>Intervention</td>
<td>Time of Measurement</td>
<td>Effect Size</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
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<tr>
<td>Forst et al. 2007b</td>
<td>10</td>
<td>12</td>
<td>Neuropathic pain (postherpetic pain (n=2), diabetic neuropathy (n=3), posttraumatic injury (n=6), CRPS (n=1))</td>
<td>Novel glutamate antagonist CNS 5161 HCl: single dose of 250 μg</td>
<td>Oral Crossover VAS pain after 12 hours</td>
<td>No significant difference in reducing pain</td>
<td>0.30 [-0.51, 1.11]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forst et al. 2007c</td>
<td>10</td>
<td>14</td>
<td>Neuropathic pain (diabetic neuropathy (n=8), posttraumatic injury (n=4), CRPS (n=2))</td>
<td>Novel glutamate antagonist CNS 5161 HCl: single dose of 500 μg</td>
<td>Oral Crossover VAS pain after 12 hours</td>
<td>No significant difference in reducing pain, (p = 0.11)</td>
<td>-0.40 [-1.15, 0.35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eichenberger et al. 2008</td>
<td>8</td>
<td>10</td>
<td>Chronic phantom limb pain after trauma (n=6) and surgery (n=4)</td>
<td>Ketamine: 0.4 mg/kg in 1 hour</td>
<td>IV Crossover VAS pain 60 min after infusion</td>
<td>Ketamine significantly reduced phantom limb pain, (p &lt; 0.001^*)</td>
<td>-1.75 [-2.06, -0.72]</td>
<td></td>
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<tr>
<td>Schwartzman et al. 2009</td>
<td>9</td>
<td>19</td>
<td>CRPS</td>
<td>Ketamine: max 0.35 mg/kg/h in 4 hours for 10 days</td>
<td>IV Parallel VAS overall pain after 2 weeks</td>
<td>Ketamine significantly reduced overall pain, (p &lt; 0.05)</td>
<td>-0.55 [-1.00, 0.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigtermans et al. 2009</td>
<td>8</td>
<td>60</td>
<td>CRPS</td>
<td>Ketamine (S+): 22.2 ± 2.0 mg/h (mean ± SD) continuously during 4.2 days</td>
<td>IV Parallel VAS pain after 1 week</td>
<td>Ketamine significantly reduced spontaneous pain, (p &lt; 0.001)</td>
<td>-5.59 [-6.76, -4.47]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finch et al. 2009</td>
<td>7</td>
<td>20</td>
<td>CRPS</td>
<td>Ketamine 10% cream</td>
<td>Topical Crossover VAS pain after 30 min</td>
<td>No significant difference in reducing pain</td>
<td>0.00 [-0.20, 0.20]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

QS: quality score, Appt: application. IV: intravenous. CRPS: complex regional pain syndrome. *: effect size estimated from significance levels, if \(p\) values were not reported \(p = 0.5\) if not significant and \(p = 0.05\) if significant were assumed. **: effect size was not estimable because no information was reported about the direction (significant or non-significant) of significance levels.
Pain Box (0–20] scale for rating pain intensity, which was transformed into a scale from 1 to 100. Positive results after treatment with NMDA receptor antagonists were reported in 13 studies [22,24,30,31,34–36,38,40,43–46]. The effects of the NMDA receptor antagonist ketamine was investigated in 11 studies [20–22,29,36,40,43–47], in which the effects of the S(+) enantiomer of ketamine was evaluated by the study of Sigtermans et al. [45], while the other 10 studies investigated racemic (R/S) ketamine. Six studies evaluated memantine [23,28,32,37,39,41], five studied the effects of dextromethorphan [27,30,32,34,38], and three studies investigated amantadine [24,25,35]. Furthermore, the effects of MgSO4 [31], MgCl2 [20], riluzole [26], GV196771 (a glycine antagonist) [33] and CNS 5161 HCl (a novel NMDA receptor antagonist) [42] were investigated. Adverse events after treatment with the different interventions are presented in Table 2.

Quantitative Analysis

In 13 studies [22–27,32,35,40,42,44–46], data (mean and SD) was available for directly calculating hedges’ g statistical analysis. Authors of the remaining studies were contacted for additional data, of whom four [20,28,38,47] provided additional data. For the remaining studies [21,29–31,33,36,37,39,41], effect sizes were calculated using P-values and t statistics (see appendix). For the study by Abraham et al. [34], no information was provided about the placebo group, therefore the individual effect size could not be estimated for this study. Three studies used different doses of NMDA receptor antagonists [26,30,42] and one evaluated more than one NMDA receptor antagonist [32]. Effect sizes for the individual studies and (different doses of) interventions are presented in Table 1.

In order to calculate the summarise effect size in comparable studies with respect to used interventions, route of administration and evaluated pain patients, studies assessing an intervention in one type of neuropathic pain patient and providing adequate data for analysis (a total of 12 studies) were categorized according to pain disorder, resulting in four pain patients groups: CRPS, postherptic neuralgia, diabetic neuropathy and postamputation pain (Figure 2). Within these pain patient groups, the summary effect size was calculated for minimum two studies evaluating the same intervention.

Summary effect sizes were calculated for subgroups of studies evaluating intravenous ketamine in CRPS patients, oral memantine in postherptic neuralgia patients and, respectively, intravenous ketamine and oral memantine in postamputation pain. The results of the two trials evaluating dextromethorphan in postamputation pain were not summarized, because the two trials (using different doses of dextromethorphan) were performed and reported within the same study, and pooling of results would therefore be questionable. Treatment with ketamine IV significantly reduced postamputation pain (pooled summary effect size: −1.18 [confidence interval (CI) 95% −1.98, −0.37], P = 0.004) (Figure 3). No significant effect on pain reduction could be established for ketamine IV in CRPS (pooled summary effect size 0.65 [CI 95% −1.47, 0.16], P = 0.11) oral memantine in postherptic neuralgia treatment (pooled summary effect size 0.03 [CI 95% −0.51, 0.56], P = 0.92) and for oral memantine in postamputation pain (pooled summary effect size 0.38 [CI 95% −0.21, 0.98], P = 0.21) (see Figures 4–6).

Discussion

Since the late 1980s, NMDA receptor antagonists have been known to decrease neuronal hyperexitability and
reduce pain, and the efficacy of several NMDA receptor antagonists has been investigated in preclinical and clinical pain studies [48]. Despite the large number of studies, there is still no consensus on the efficacy of NMDA receptor antagonist on neuropathic pain therefore the present systematic review was performed.

We found several randomized placebo controlled studies investigating the effects of a variety of interventions on a diversity of neuropathic pain patients. In order to pool or summarize results to achieve an overall estimation of the effectiveness of a therapeutic intervention, studies have to be similar in the used intervention, route of administration and the investigated patients. Only half of the found studies evaluated the intervention in one type of neuropathic pain patient [21,23–25,28,30–32,35–37,39,41,43–45,47], of which only a few evaluated the same NMDA receptor antagonists using same routes of administration in patients with similar neuropathic pain etiologies. Consequently, we could only summarize the results of two studies investigating ketamine IV in CRPS [44,45], two studies evaluating oral memantine in postherptic neuralgia [23,32] and, respectively, two studies investigating ketamine IV [21,43] and two studies evaluating oral memantine in postamputation pain [37,39]. Ketamine IV was shown to have a large effect [19] in reducing postamputation pain. Based on the small number of pooled results and the lack of information...
about the effects of other NMDA receptor antagonists besides ketamine and memantine on other pain conditions, we consider it speculative to draw definite conclusions about the efficacy of NMDA receptor antagonists on neuropathic pain. Further, RCTs including well-defined neuropathic pain disease groups are needed to elucidate the effects of NMDA receptor antagonists on neuropathic pain.

**Figure 3** Intravenous ketamine versus placebo in postamputation pain. $I^2 = 0\%$. Pooled summarized effect size, fixed effect model: $-1.18$ (confidence interval $95\%$ $-1.98$, $-0.37$), $P = 0.004$.

**Figure 4** Intravenous and topical ketamine versus placebo in CRPS. $I^2 = 55\%$. Pooled summarized effect size, random effect model: $-0.65$ (confidence interval $95\%$ $-1.47$, $0.16$), $P = 0.11$. 
Besides increasing the ability to compare and/or pool individual studies, examining just one type of pain patient also increases the homogeneity of the investigated sample and therefore reduces bias within a study. Neuropathic pain consists of a very heterogeneous group of patients regarding the type and degree of their complaints [49]. This heterogeneity could also be expressed in the composition of the NMDA receptor. The NMDA receptor is

**Figure 5** Oral memantine versus placebo in postherpetic neuralgia. $I^2 = 0\%$. Pooled summarized effect size, fixed effect model: 0.03 (confidence interval 95% -0.51, 0.56), $P = 0.92$.

**Figure 6** Oral memantine versus placebo in postamputation pain. $I^2 = 0\%$. Pooled summarized effect size, fixed effect model: 0.38 (confidence interval 95% -0.21, 0.98), $P = 0.21$. 
collins et al.

constructed of different subunits (NR1, NR2A-D and NR3A-C), which can be combined in different ways (NR1 in combination with 2A-D or 3A-C) [48,50]. The different subtype combinations are known to have distinct biophysical and pharmacological characteristics [51], which may influence binding of NMDA receptor antagonists. In addition, NMDA receptor antagonists are known to differ in their NMDA subtype selectivity and affinity for specific combinations of NMDA receptor subtypes. At present, little is known about the NMDA subtype pattern in different neuropathic pain disorders. The expression of different subtype combinations may result in different selectivity and binding sensitivities for NMDA receptor antagonists, which may lead to differences in pain relief. Research in which the effects of NMDA receptor antagonists are evaluated in homogenous groups of neuropathic pain patients is therefore required to assess possible disease related differences in treatment effects of NMDA receptor antagonists.

In this meta-analysis, we evaluated pain in neuropathic pain patients. Neuropathic pain has recently been redefined by the International Association for the Study of Pain as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [1]. Conditions without a clearly demonstrated lesion or disease affecting the somatosensory nervous system, such as fibromyalgia, are not considered neuropathic pain. In the past, there has been some discussion about CRPS being a neuropathic pain syndrome. We have included studies on CRPS patients, as recent findings of peripheral pathological changes [52] and damage in the innervations of the skin in CRPS [53,54] support the concept of CRPS being a peripheral neuropathic condition. In fibromyalgia patients, no physical or biological findings have yet been made that relate directly to a lesion or disease of the somatosensory system. However, abnormally enhanced temporal summation of second pain, expansion of receptive fields, hyperalgesia after electrical stimulation, and late evoked potentials have been described in these patients [55–57]. These central hyper-sensitivities are indicative of the existence of central sensitization, suggestive of the presence of a neuropathic component in fibromyalgia. NMDA receptor antagonists were shown to reduce pain in fibromyalgia [58]. Further research is warranted to determine the effects of NMDA receptor antagonists in fibromyalgia and other disorders with features of neuropathic pain.

Ketamine is probably the most investigated NMDA receptor antagonists for the treatment of neuropathic pain [48], which explains the large number of trials using ketamine in our review. Ketamine is known to equally bind the NMDA subtypes 2A to 2D and may therefore have a more favorable effect in such a heterogenic disease as neuropathic pain, compared with NMDA receptor antagonists with more discriminative NMDA subtype selectivity. In addition, ketamine is a high affinity NMDA receptor antagonist, resulting in long-term blocking of the receptor and strong inhibiting of the neuronal hyperexcitability occurring in neuropathic pain. A disadvantage of this undiscriminating and strong binding property, however, is the higher proportions of side effects due to binding of the antagonists to neuronal structures not involved in pain.

The use of the S(+)-enantiomer of ketamine in clinical trials [45], may be favorable regarding side effects. S(+) ketamine is twice as potent in analgesic effect compared with racemic ketamine [59]; therefore, lower doses of S(+) ketamine may reduce side effects, while providing pain reduction resembling racemic ketamine. In the present review, a statistically significant effect in reducing neuropathic pain for ketamine was only found for post-amputation pain. Evaluation of the individual effect sizes, however, revealed five large effect trials [19], in which ketamine was used in four trials (in patients with post-amputation pain [21,43], posttraumatic, postherptic neuralgia [36], and CRPS [45], respectively). Therefore, we argue that ketamine (and especially S(+)-ketamine) may be a promising intervention for pain relief in neuropathic pain. In this respect, a reservation has to be made with regard to the inclusion of an article by a member of our group [45], therewith introducing possible interpretation bias. However, quality assessments for this article were not performed by those directly involved in the study in question. Furthermore, omitting this article from the analysis would not have lead to significantly different conclusions.

Our methodology only considers spontaneous pain as outcome measurement after treatment with NMDA receptor antagonists. Many studies found in this review also investigated the effects of NMDA receptor antagonists on evoked pain (allodynia, hyperalgesia, windup pain) [22–27,30,35,40,42–44,47]. These studies used various stimulus modalities of different strengths to evoke pain. In order to diminish the heterogeneity and make comparison of different interventions possible, we only used spontaneous pain as outcome measurement. Consequently, we have no information about the effects of NMDA receptor antagonists on other aspects of sensitization. Possibly, some antagonists may affect spontaneous pain, allodynia or hyperalgesia in a different manner. Further (meta-analytic) research may elucidate the effects on NMDA receptor antagonists on other aspect of sensitization.

Another methodological consideration in this study is the fact that only comparisons between NMDA receptor antagonists and placebo were taken into account. Comparisons with active (real) interventions could possibly lead to lower effect sizes than those found in the present meta-analysis. On the other hand, one should bear in mind that effect sizes in general will be negatively influenced by the heterogeneity of the included studies, thereby limiting their magnitude.

Conclusions

Based on the results found in this systematic review, no conclusions can be made about the efficacy of NMDA
receptor antagonists on neuropathic pain. However, evi-
dence in favor of the effectiveness of NMDA receptor
antagonists for the treatment of neuropathic pain, of which
ketamine seems to be the most potent, is accumulating.
Additional randomized placebo controlled studies in
homogenous groups of pain patients are needed to explore
the therapeutic potential of NMDA receptor antagonists in
neuropathic pain.

Acknowledgments

We would like to express our gratitude to Ingrid Riphagen,
MSc (Medical Library, VU University, Amsterdam, the
Netherlands) for her expertise and support in searching
the literature and to Prof Dr Riekie de Vet (EMGO+
Institute

for Health and Care Research, Amsterdam, VU University
Medical Center Amsterdam, the Netherlands) for her
advice with regard to the methodological assessment.
This study is part of TREND (Trauma RERelated Neuronal
Dysfunction), a knowledge consortium that integrates
research on Complex Regional Pain Syndrome type 1
(CRPS-1). This project is supported by a Dutch Govern-
ment grant (BSIK03016).

Appendix [15,16,18,60–63]

Calculating Hedges’ g from the Mean, Standard
Deviation and Number of Subjects

\[
g_i = \frac{(M_e - M_c)}{SD \text{ pooled}}
\]

\[
SD \text{ pooled} = \sqrt{\left(\frac{\left[\frac{((SD_e)^2(n_e - 1)) + (SD_c)^2(n_c - 1))}{(n_e + n_c) - 2}\right]}{\left[\frac{((SD_e)^2(n_e - 1)) + (SD_c)^2(n_c - 1))}{(n_e + n_c) - 2}\right]}\}
\]

Where, \( g_i \) = hedges’ g for individual study i, \( M \) = mean,
\( e \) = experimental group, \( c \) = control group, \( SD \) = standard
deviation, \( n \) = sample size in a particular group.

Calculating Hedges’ g from the t-Test

\[
g_i = \frac{t\sqrt{(n_e + n_c)}}{\sqrt{\left(\frac{1}{n_e} + \frac{1}{n_c}\right)}}, \text{ and when } n_e \text{ and } n_c \text{ are equal } g_i = 2t/\sqrt{N}
\]

Where, \( t \) = value of the t-test, \( N \) = total sample size.

Calculating Hedges’ g, from Significance Levels

When only P-values are reported, t-values can be
obtained using a calculator or looked up in a table of
the t distribution using P-levels and the degrees of
freedom. From the t-test, hedges’ g can be calculated
(see above).

Calculating 95% Confidence Intervals (CI) for
Hedges’ g

\[
CI = \pm 1.96 \text{ (two-tailed and a critical value at 0.05) } \times \sqrt{V_i}
\]

\[
V_i = \left(\frac{N_i}{n_i} \cdot n_i \cdot (g_i^2/2N)\right)
\]

Where \( V_i \) = within-study variance of individual effect size i.

NMDA Receptor Antagonists for Neuropathic Pain

Calculating Summarized Effect Size Hedges’g
According to Fixed Effect Model

\[
g_s = \sum g_i \cdot W_i \cdot \sum W_i
\]

\[
W_i = 1/\sqrt{V_i}
\]

Where, \( g_s \) = summarized hedges’ g, \( W_i \) = estimated
weight for individual study i.

Calculating Homogeneity Statistics \( I^2 \)

\[
I^2 = \text{ proportion of total variability explained}
\]

\[
by heterogeneity
\]

\[
I^2 = \frac{(Q - (k - 1))/Q}{100\%}, \text{ for } Q > (k - 1)
\]

\[
I^2 = 0, \text{ for } Q \leq (k - 1)
\]

\[
Q = \sum W_i g^2 - \left(\frac{\sum W_i g^2}{\sum W_i}\right)^2
\]

\[
Q = Q \text{ statistics}
\]

A random effect model must be used when the pooled
effects of studies could be considered heterogeneous
\( I^2 \) statistics \( \geq 25\% \).

Calculating Summarized Effect Size Hedges’g
According to Random Effects Model

\[
g_s = \sum g_i W_i \cdot \sum W_i
\]

\[
W_i = 1/\sqrt{V^*}
\]

\[
V_i^* = \sigma_i^2 + \frac{1}{\sqrt{N}}
\]

\[
\sigma_i^2 = \frac{(Q - (k - 1))/c,}{c = \sum W_i - ((\sum W_i)^2/\sum W_i)}
\]

Where \( V^* \) = total variance, \( \sigma_i^2 \) = between study variance,
\( Q = Q \text{ statistics}, \ k = \text{ number of studies in the meta-}
analysis.\n
Calculating 95% CI for \( g_s \)

\[
CI = \pm 1.96 \text{ (two-tailed and a critical value at 0.05) } \times \sqrt{\frac{V_s}{\sqrt{N}}}
\]

Where, \( V_s \) = variance of summarized effect size.

Calculating P-Values for \( g_s \)

\[
Z = |g_s| \sqrt{\frac{V_s}{N}}
\]

Where, \( Z = Z\text{-value}.\n\]

\( P\) values can be obtained using \( Z\) table.

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