Ketamine's second life : Treatment of acute and chronic pain

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Section II

Review

Chapter 2

Meta-analysis of NMDA receptor antagonists for the treatment of neuropathic pain

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Submitted

2.1 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 aetiologies such as post-herpetic neuralgia, diabetic neuropathy, and Complex Regional Pain Syndrome.[2] Symptoms associated with neuropathic pain are allodynia, hyperalgesia and spontaneous pain. A number of mechanisms have been described that may contribute to the generation of neuropathic pain. Examples include nociceptor sensitization, ectopic excitability of sensory neurons, alterations in ion channel expression on the peripheral level and spinal and/or cortical reorganization, changes in inhibitory pathways and central sensitization on the central level.[3–5] 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 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 antagonists on neuropathic pain patients of various aetiologies 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 is to perform meta-analysis evaluating the effects of NMDA antagonists on neuropathic pain. Furthermore, subgroup analyses will be performed in assessing the effects of individual NMDA antagonists on neuropathic pain and their response on individual neuropathic pain disorders, testing the hypothesis that NMDA antagonists are effective in the treatment of pain in neuropathic pain patients.

2.2 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.

Search strategy

We searched the PubMed (including MEDLINE), EMBASE (Elsevier Embase.com) databases and Cochrane Central Register of Controlled Trials (CENTRAL) up to October 26th, 2009 for studies written in the English, German or Dutch language. In PubMed MeSH terms ('Receptors, N-Methyl-D-Aspartate/antagonists and inhibitors', "N-Methylaspartate/antagonists and inhibitors", "Pain", "Analgesia", "Analgesia Patient–Controlled", "Analgesics", "Hyperalgesia", "Sensation", "Proprioception") were used as well as free text terms ("nmda, N-Methyl-D-Aspartate" , "inhibit*", "block*" , "antagoni*", "pain", "pains", "analgesi*", "hyperalgesi*", "allodynia", "hyperaesthesia", "hyperesthesi*", "ache", "aches", "neuralgi*", "neuropath*", "sensitization", "sensitization", "arthralgi*", "proprioception", "sensation", sciatica", "metatarsalgia"). In addition, a RCT search filter recommended by the Cochrane Collaboration was used.[12] EMBASE was searched with the EMtree terms: "n Methyl dextro aspartic acid receptor blocking agent", "Pain", "Analgesia", and "Analgesic agent". CENTRAL was searched with the search terms: nmda and "N Methyl D Aspartate" linked to inhibition*, inhibited, inhibit, block* and antagoni*, as well as the search terms pain, pains, analgesi*, hyperalgesi*, allodynia, hyperaesthesi*, hyperesthesi*, ache, aches, neuralgi*, neuropath*, sensitization, sensitization, arthralgi*, proprioception, sensation, sciatica and metatarsalgia.

Quality assessments

In order to determine the quality of the studies, identified studies were independently scored by the authors SC and MS using the Delphi list.[13] The Delphi list consists of nine items, with addition of two criteria ("Were the outcome measurements described clearly" and "Were adverse events described?") to ascertain the methodological and clinical accuracy of the trials. All criteria were scored with yes (=1), no (=0), or don't know (0), with equal weights given to all criteria. The number of positive scores contributed to the quality scores, ranging from 0 to 11. Disagreements were solved by consensus and if necessary by third party (R.P.), studies with scores of 6 or higher were considered as good quality studies.[14]

Quantitative analysis

The studies were analyzed in RevMan 5 using the effect size Hedges' g (standardized mean difference),[15] 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. A heterogeneity test statistics I^2 was determined to assess whether a fixed or random effects model was appropriate to calculate the summary effect size using Hedges' g.[16,17] A fixed effect model was used when the pooled effects of studies could be considered homogeneous (I^2 statistics below 25%).[17] The difference in pain relief between experimental and placebo 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

Table 2.1: The Delphi list

Item	Delphi list	Yes	No	Unknow
1	Was a method of randomization performed?			
2	Was the treatment allocation concealed?			
3	Where the groups similar at baseline regarding the most prognostic indicators?			
4	Were the eligibility criteria specified?			
5	Was the outcome assessor blinded?			
6	Was the care provider blinded?			
7	Was the patient blinded?			
8	Were point estimates and measures of variability presented for the primary outcome measurements?			
9	Did the analysis included an intention to treat analysis?			
10	Were the outcome measurements described clearly?			
11	Were adverse events described?			

of these articles. For each study a weighting factor 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 to 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 comparable studies, evaluating the effects of 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[18] 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.

2.3 Results

Quality of studies

Twenty-seven studies were included meeting the inclusion criteria (figure 2.1).[19–45] One included study was written by MS,[43] 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 0.09). The studies were of good quality (median

quality score 8 (IQR 7-9)) (table 2.1), except for the studies of Furuhashi-Yonaha[30] and Schiffito[21] in which a quality score of respectively 2 and 3 were found.

Description of studies

Twenty-two studies were of a crossover design and in 5 studies a parallel design was used (table 2.1). In 2 studies active placebo (loraxepam) were used.[23,35] The interventions were evaluated in 552 neuropathic pain patients of various aetiologies (Complex Regional Pain Syndrome n=106; 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; Post traumatic 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 NRS (0-10 or 0-100) scores except for the study of Sang et al which used the Gracely 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.[20,22,24–26,30,32,36,40–43,45]
The effects of the NMDA antagonist ketamine was investigated in 10 studies, in which the effects of the S(+) enantiomer of ketamine was evaluated by the study of Sigtermans *et al.*,[43] while the other nine studies investigated racemic (R/S) ketamine.[28,30,32,34,36,38,40,42,45] Six studies evaluated memantine,[19,21,27,33,35,44] 5 studied the effects of dextromethorphan,[23,24,26,35,46] and 3 studies investigated amantadine.[22,25,39] Furthermore, the effects of MgSO4,[20] MgCl2,[28] riluzole,[31] GV196771 (a glycine antagonist),[37] and CNS 5161 HCl (a novel NMDA antagonist)[29] were investigated. Adverse events after treatment with the different interventions are presented in table 2.2.

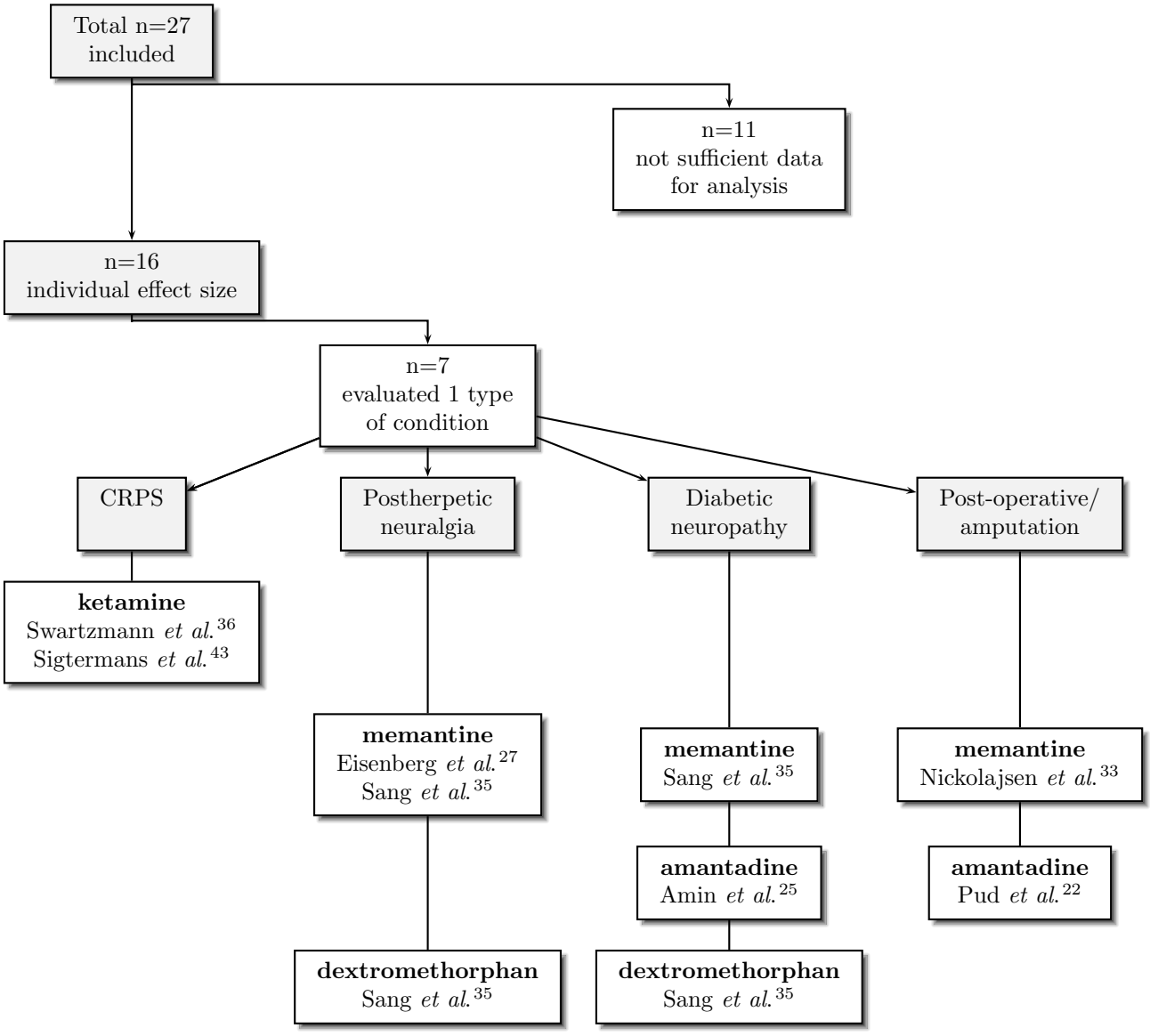

Figure 2.1: Flow chart of study selection

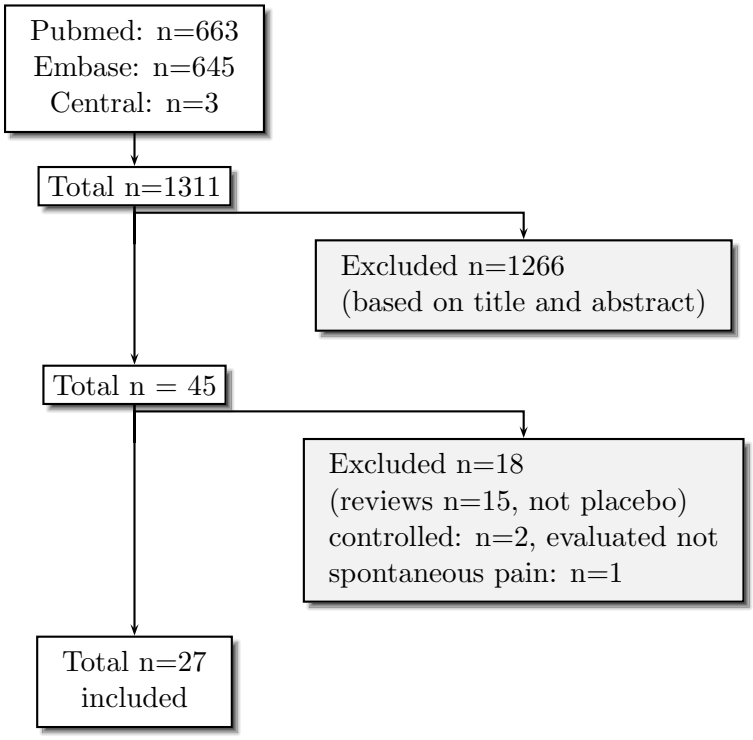

Figure 2.2: Flow chart of study selection

Table 2.2: Included studies

Authors	Quality Score	N	Patients	Interventions	Appl	Design	Primary outcome	Results	Individual effect size (inverse variance)
Max *et al.*[32]	7	7	Posttraumatic pain and allodynia	Ketamine: 2h, 0.75mg/kg/h	IV	Crossover	VAS pain after 2 hours	Background pain after 2h, p=0.001	-0.82 [-1.93, 0.29]
Felsby *et al.*[28]	8	10	Chronic neuropathic pain (after amputation (n=3), after operation (n=5), after radiation (n=2))	Ketamine: 10 min, 0.2mg/kg and 50 min, 0.3mg/kg/h	IV	Crossover	VAS pain 15 min after infusion	Pain intensity, 15 min after infusion, p=0.006	-0.40 [-1.29, 0.49]
Felsby *et al.*[28]	8	10	Chronic neuropathic pain (after amputation (n=3), after operation (n=5), after radiation (n=2))	MgCl2: 10 min, 0.16 mmol/kg and 50 min 0.16 mmol/kg/h	IV	Crossover	VAS pain 15 min after infusion	Pain intensity, 15 min after infusion, p=0.084	-0.28 [-1.16, 0.60]
Nickolajsen *et al.*[34]	8	11	Post amputation stump and phantom limb pain	Ketamine: bolus 0.1mg/kg/5min and 7μg/kg/min for 40 min	IV	Crossover	VAS pain after infusion	Ketamine produced a significant relief of stump and phantom pain	Not estimable
Eisenberg *et al.*[27]	10	20	Postherpetic neuralgia	Memantine: wk 1:10mg/d, wk 2/5: 20mg/d	Oral	Parallel	VAS (0-10) pain after 5 weeks	No statistically significant difference in reduction of pain	0.22 [-0.66, 1.10]
Pud *et al.*[22]	7	13	Surgical neuropathic pain in cancer patients	Amantadine: 200mg in 3 hours	IV	Crossover	VAS pain after treatment	Amantadine significantly reduced pain	-1.41 [-2.28, -0.54]
Medrik-Goldberg *et al.*[39]	9	30	Sciatica	Amantadine: 2.5 mg/kg in 2 hours	IV	Crossover	VAS pain after 180 min	No significant difference between amantadine and placebo in reducing spontaneous pain	0.04 [-0.47, 0.54]
Galer *et al.*[31]	9	22	Peripheral neuropathic pain (postherpetic neuralgia (n=13), diabetic polyneuropathy (n=1), peripheral neuropathy other than diabetic (n=8))	Riluzole: 100mg/d for 2 weeks	Oral	Crossover	VAS pain after 2 weeks	Doses of 100mg/d not effective in alleviating peripheral neuropathic pain	0.26 [-0.33, 0.85]
Galer *et al.*[31]	9	21	Peripheral neuropathic pain (postherpetic neuralgia (n=9), diabetic polyneuropathy (n=1), peripheral neuropathy other than diabetic (n=11))	Riluzole: 200mg/d for 2 weeks	Oral	Crossover	VAS pain after 2 weeks	Doses of 200mg/d not effective in alleviating peripheral neuropathic pain	-0.07 [-0.67, 0.54]
Gilron *et al.*[23]	8	16	Facial neuralgias (possible trigeminal neuropathy (n=10), anaesthesia dolorosa (n=4), idiopathic trigeminal neuralgia (n=2))	Dextromethorphan: 120mg/d, titrated to max 920mg/d for 6 weeks	Oral	Crossover	VAS overall daily pain after 6 weeks	Dextromethorphan shows little or no analgesic efficacy in pain	0.05 [-0.65, 0.74]
Nickolajsen *et al.*[33]	7	15	Neuropathic pain after amputation (n=12) or operation (n=3)	Memantine: wk 1: 5mg/d, wk 2: 10mg/d, wk 3: 15mg/d, wk4/5: 20mg/d	Oral	Crossover	VAS (0-10) pain during wk4/5	No significant difference between placebo and memantine in reducing spontaneous pain	-0.41 [-1.06, 0.23]
Leung *et al.*[38]	7	12	Neuropathic pain (postherpetic neuralgia (n=4), CRPS (n=7), spinal cord injury (n=1))	Ketamine: target plasma levels of 50, 100 and 150ng/ml	IV	Crossover	VAS pain at 3 plasma levels	No significant reduction in spontaneous pain	Not estimable
Abraham *et al.*[24]	8	3	Phantom pain in cancer amputees	Dextromethorphan: 1 wk 120mg/d	Oral	Crossover	VAS pain after 1 week	Dextromethorphan effectively reduced post amputation phantom limb pain	Not estimable

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Table 2.2 – Continued

Authors	Quality Score	N	Patients	Interventions	Appl	Design	Primary outcome	Results	Individual effect size (inverse variance)
Abraham *et al.*[24]	8	3	Phantom pain in cancer amputees	Dextromethorphan: 1 wk 180mg/d	Oral	Crossover	VAS pain after 1 week	Dextromethorphan effectively reduced post amputation phantom limb pain	Not estimable
Brill *et al.*[20]	9	7	Postherpetic neuralgia	MgSO4: 30mg/kg MgSO4 in 30 min	IV	Crossover	VAS pain after 30 minutes	MgSO4 was effective in reducing pain in postherpetic neuralgia	Not estimable
Furuhashi-Yonaha *et al.*[30]	2	8	Neuropathic pain patients that have been relieved by intravenous ketamine (CRPS (n=4), visceral pain (n=2), postherpetic neuralgia (n=1), phantom limb pain (n=1))	Ketamine: 0.5mg/kg every six hours for a week	Oral	Crossover	VAS pain after 1 week	Oral ketamine reduced severity of the pain	-1.45 [-2.59, -0.31]
Sang *et al.*[35]	8	19	Diabetic neuropathy	Dextromethorphan: 7 wk titration till max tolerated doses and 2 wk maintenance, median doses 400mg/d	Oral	Crossover	Gracely Box Scale (37) during last week of treatment period	Dextromethorphan was not significantly better than (active) placebo	-0.43 [-1.08, 0.21]
Sang *et al.*[35]	8	17	Postherpetic neuralgia	Dextromethorphan: 7 wk titration till max tolerated doses and 2 wk maintenance, median doses 400mg/d	Oral	Crossover	Gracely Box Scale during last week of treatment period	Dextromethorphan was not significantly better than (active) placebo	-0.06 [-0.70, 0.57]
Sang *et al.*[35]	8	19	Diabetic neuropathy	Memantine: 7 wk titration till max tolerated doses and 2 wk maintenance, median doses 55 mg/d	Oral	Crossover	Gracely Box Scale during last week of treatment period	Memantine was not significantly better than (active) placebo	-0.03 [-0.71, 0.64]
Sang *et al.*[35]	8	17	Postherpetic neuralgia	Memantine: 7 wk titration till max tolerated doses and 2 wk maintenance, median doses 55 mg/d	Oral	Crossover	Gracely Box Scale during last week of treatment period	Memantine was not significantly better than (active) placebo	-0.01 [-0.68, 0.66]
Wallace *et al.*[37]	7	62	Neuropathic pain (postherpetic neuralgia (n=26), peripheral nerve injury (n=21), CRPS (n=9), diabetic neuropathy (n=6))	Glycine antagonist GV196771: 2 weeks 300 mg/d	Oral	Parallel	VAS pain at the end of 2 week treatment	No significant effect of GV196771 on spontaneous pain	Not estimable
Abraham *et al.*[41]	6	10	Phantom pain in cancer (n=8) and non cancer (n=2) amputees	Dextromethorphan: 10 days 120mg/d	Oral	Crossover	VAS pain after 10 days	All patients reported a ¿ 50% decrease in pain intensity after treatment	Not estimable
Abraham*et al.*[41]	6	10	Phantom pain in cancer (n=8) and non cancer (n=2) amputees	Dextromethorphan: 10 days 180mg/d	Oral	Crossover	VAS pain after 10 days	All patients reported a ¿ 50% decrease in pain intensity after treatment	Not estimable
Amin *et al.*[25]	8	17	Diabetic peripheral neuropathy	Amantadine: 1x 200 mg in 500 ml 0.9% NaCl	IV	Crossover	VAS pain after 1 week	Amantadine significantly decreased pain intensity after 1 week	-0.77 [-1.47, -0.07]

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Table 2.2 – Continued

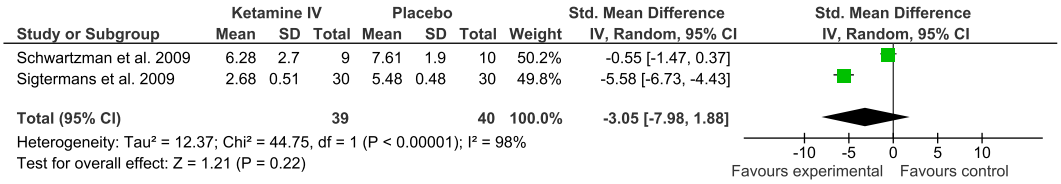
Authors	Quality Score	N	Patients	Interventions	Appl	Design	Primary outcome	Results	Individual effect size (inverse variance)
Jorum *et al.*[40]	7	12	Post traumatic neuralgia (n=11) and postherpetic neuralgia (n=1)	Ketamine: bolus 60μg/kg and 6μg/kg for 20min	IV	Crossover	VAS pain after infusion	Ongoing pain was significantly reduced after ketamine infusion	Not estimable
Maier *et al.*[19]	11	16	Chronic phantom limb pain after amputation of arm or leg	Memantine: week 1 titration 30mg/d: 5mg/d + added 5mg daily, w2+3: 30mg/d	Oral	Crossover	VAS pain after 3 weeks	No significant clinical effect of memantine in chronic phantom limb pain	Not estimable
Carlsson *et al.*[26]	7	13	Neuropathic pain of traumatic origin	Dextromethorphan: 1x 270 mg	Oral	Crossover	VAS pain after 0-4 hours	Dextromethorphan has an analgesic effect in patients with neuropathic pain of traumatic origin	-0.76 [-1.56, 0.04]
Wiech *et al.*[44]	8	8	Chronic phantom limb pain	Memantine: wk 1: 10mg/d, wk 2: 20 mg/d, wk 3/4: 30mg/d	Oral	Crossover	VAS pain after 4 weeks treatment	Memantine had no effect on intensity of chronic limb pain Not estimable	
Gottrup *et al.*[42]	8	10	Verified nerve injury pain	Ketamine: bolus 0.1mg/kg in 10min and 0,007 mg/kg/min in 20min	IV	Crossover	VAS pain during infusion	Ketamine significantly reduced ongoing pain	-0.35 [-0.99, 0.29]
Schifitto *et al.*[21]	3	45	HIV associated sensory neuropathy	Memantine: wk 1: 10mg/d + added weekly for 4 wk 10mg/d, wk 4/16: 40 mg/d	Oral	Parallel	VAS pain after 16 weeks	Memantine is ineffective in reducing HIV associated sensory neuropathy	Not estimable
Frost *et al.*[29]	10	12	Neuropathic pain (postherpetic pain (n=3), posttraumatic injury (n=6), CRPS (n=3))	CNS 5161 HCl: single dose of 125μg	Oral	Crossover	VAS pain after 12 hours Treatment with 125μg	CNS 5161 provides no indications of analgesic activity	0.11 [-0.64, 0.85]
Frost *et al.*[29]	10	12	Neuropathic pain (postherpetic pain (n=2), diabetic neuropathy (n=3), posttraumatic injury (n=6), CRPS (n=1))	CNS 5161 HCl: single dose of 250μg	Oral	Crossover	VAS pain after 12 hours Treatment with 250μg	CNS 5161 provides no indications of analgesic activity	0.43 [-0.32, 1.19]
Frost *et al.*[29]	10	14	Neuropathic pain (diabetic neuropathy (n=8), posttraumatic injury (n=4), CRPS (n=2))	CNS 5161 HCl: single dose of 500μg	Oral	Crossover	VAS pain after 12 hours	Treatment with 500μg CNS 5161 provides some indications of analgesic activity	-0.24 [-0.99, 0.50]
Eichenberger *et al.*[45]	8	10	Chronic phantom limb pain after trauma (n=6) and surgery (n=4)	Ketamine: 0.4 mg/kg in 1 hour	IV	Crossover	VAS pain after infusion	Ketamine significantly reduced phantom limb pain	Not estimable
Schwartzman[36]	9	19	CRPS	Ketamine: max 0.35 mg/kg/h in 4 hours for 10 days	IV	Parallel	VAS overall pain after 2 weeks	Ketamine significantly reduced overall pain	-0.55 [-1.47, 0.37]
Sigtermans[43]	8	60	CRPS	Ketamine (S+): 22.2 $\pm$ 2.0 mg/h (mean SD) continuously during 4.2 days	IV	Parallel	VAS pain after 12 weeks	Ketamine significantly reduced spontaneous pain	-5.58 [-6.73, -4.43]

Table 2.3: Adverse events of interventions

Intervention	Adverse events
Ketamine	Sedation, dreams, hallucinations, dissociative reaction, nausea, headache, dizziness, fatigue, changes in mood, altered sight, feeling of unreality, dry mouth, lightheadedness, paresthesia, changed taste, dysarthria, euphoria, tinnitus, drunkenness, itching, muteness, and hyperventilation.
Memantine	Nausea, fatigue, dizziness, agitation, headache, sedation, dry mouth, gastrointestinal distress, anorexia, constipation, vertigo, restlessness, excitation, insomnia, blurred vision and tinnitus.
Amantadine	Nausea.
Dextromethorphan	Cognitive impairment, dizziness, ataxia, lightheadedness, drowsiness, vision disturbances, euphoria, hot flushes, nausea, speaking difficulties, unpleasantness, numbness, concentration problems, shivers, vomiting, itching, dry mouth, tinnitus, rash, sedation, gastrointestinal distress and anorexia.
GV 196771	Dizziness.
CNS 5161 HCl	Headache, blurred vision, flatulence, dyspepsia, abdominal comfort and nausea.
$MgSO_4$	Mild feeling of warmth at the site of infusion.
$MgCl_2$	Heat sensations, injection pain and sedation.
Riluzole	Not mentioned.

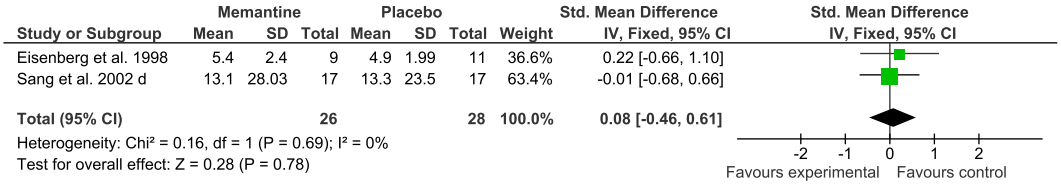
Quantitative analysis

In 13 studies[22,23,25,27,29–32,35,36,39,42,43] data was available for statistical analysis. Authors of the remaining studies were contacted for additional data, of whom three[26,28,33] provided additional data. All of these studies had quality scores of 6 or higher. The individual effect sizes were calculated for these 16 studies. Two studies used different doses of NMDA antagonists[29,31] and one evaluated more than one NMDA antagonist.[35] Effect sizes for the individual interventions are presented in table 2.1.
In order to calculate the summarize effect size in comparable studies with respect to used interventions and evaluated pain patients, studies assessing an intervention in one type of neuropathic pain patient and providing adequate data for analysis (a total of 7 studies) were categorized according to pain disorder, resulting in 4 pain patients groups: CRPS, postherpetic neuralgia, diabetic neuropathy and post-operation/amputation pain (figure 2.2). Within these pain patient groups, the summary effect size was calculated for minimum 2 studies evaluating the same intervention.



(a) Intravenous ketamine versus placebo in CRPS

Figure 2.3: I^2: proportion of Total variability explained by heterogeneity, Z: z-score



(a) Oral memantine versus placebo in Postherpetic neuralgia

Figure 2.4: I^2: proportion of Total variability explained by heterogeneity, Z: z-score

The summary effect size of intravenous ketamine could be calculated for CRPS patients and oral memantine for postherpetic neuralgia patients. No significant effect on pain reduction could be established for both the ketamine i.v. in CRPS (pooled summary effect size -3.05 (95% CI -7.98, 1.88), p = 0.22) and the oral memantine in postherpetic neuralgia treatment (pooled summary effect size 0.08 (95% CI -0.46, 0.61), p = 0.78) (see figure 2.3 and 2.4).

2.4 Discussion

Since the late 1980s, NMDA antagonists have been known to decrease neuronal hyperexitability and reduce pain, and has the efficacy of several NMDA antagonists been investigated in preclinical and clinical pain studies.[47] Despite the high number of studies, there is still no consensus on the efficacy of NMDA 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 higher levels of accuracy and precision in calculating the relative merit of therapeutic interventions, studies have to be similar in the used intervention and the investigated patients. Only half of the found studies evaluated the intervention in one type of neuropathic pain patient,[19–21,25,27,35,36,39,40,43–45] of which only a few provided sufficient data.[25,27,35,36,39,43] Most of the other trials included patients with various neuropathic pain aetiologies. As a result, we could only perform the results of 2 studies investigating ketamine i.v. in CRPS and 2 studies examining oral memantine in postherpetic neuralgia, in which the interventions were shown to have no effect. Based on the small number of pooled results and the lack of information about the effects of other NMDA antagonists on other pain conditions it is speculative to draw definite conclusions about

the efficacy of NMDA antagonists on neuropathic pain. Further randomized placebo controlled trials including well defined neuropathic pain disease groups are needed to elucidate the effects of NMDA antagonists on neuropathic pain. 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 reduces therewith bias within a study. Neuropathic pain consists of a very heterogeneous group of patients regarding the type and degree of their complaints.[48] This heterogeneity could also be expressed in the composition of the NMDA receptor. The NMDA receptor is constructed of different subunits (NMDA1, 2A-D and 3A-C), which can be combined in different ways (NMDA1 in combination with 2A-D or 3A-C).[47,49] The different subtype combinations are known to have distinct biophysical and pharmacological characteristics,[50] which may influence binding of NMDA antagonists. In addition, NMDA 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 subunit combinations may result in different selectivity and binding sensitivities for NMDA antagonists, which may lead to differences in pain relief. Research in which the effects of NMDA antagonists are evaluated in homogeneous groups of neuropathic pain patients is therefore required to assess possible disease related differences in treatment effects of NMDA antagonists. In this meta-analysis we evaluated pain in neuropathic pain patients. Neuropathic pain has recently been redefined by the IASP 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[46] and damage in the innervation of the skin in CRPS[51,52] 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, abnormal enhanced temporal summation of second pain, expansion of receptive fields and hyperalgesia after electrical stimulation and late evoked potentials have been described in these patients.[53–55] These central hypersensitivities are indicative for the existence of central sensitization, suggestive for the presence of a neuropathic component in fibromyalgia. NMDA antagonists were shown to reduce pain in fibromyalgia.[56] Further research is warranted to determine the effects of NMDA antagonists in fibromyalgia and other disorders with features of neuropathic pain. Ketamine is probably the most investigated NMDA antagonists for the treatment of neuropathic pain,[47] which explains the high 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 favourable effect in such a heterogenic disease as neuropathic pain, compared to NMDA 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,[43] may be favourable regarding side effects. S(+) ketamine is twice as potent in analgesic effect compared to racemic ketamine,[57] therefore lower doses of S(+) ketamine may reduce side effects, while providing pain reduction resembling racemic ketamine. Although, no statistically significant effect for ketamine in reducing neuropathic pain was found in the present review, evaluation of the individual effect sizes revealed 4 large effect[18] trials, in which ketamine was used in 3 trials. Therefore, we think 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,[43] 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 antagonists. Many studies found in this review also investigated the effects of NMDA antagonists on evoked pain (allodynia, hyperalgesia, windup pain).[22–25,27,29,31,32,36,39,42,45] 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 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 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 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, therewith limiting their magnitude.

Conclusion

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

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