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NEUROPATHIC PAIN SECTION

Review Article

NMDA Receptor Antagonists for the Treatment of Neuropathic Pain

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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 postherptic 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 postherptic 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

[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 and 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 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.

Search Strategy

PubMed (including MEDLINE) (from 1966 to October 26, 2009), EMBASE (Elsevier Embase.com) (from 1980 to October 26, 2009) and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched 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 randomized placebo controlled trials (RCTs) search filter recommended by the Cochrane Collaboration was used [12].

EMBASE was searched with the EMtree terms: "n Methyl d 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 a third party (RP), studies with scores of 6 or higher were considered as good quality studies [14].

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 I^2 [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

pooled effects of studies could be considered homogenous (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 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 [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 0.09). 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; postherptic 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

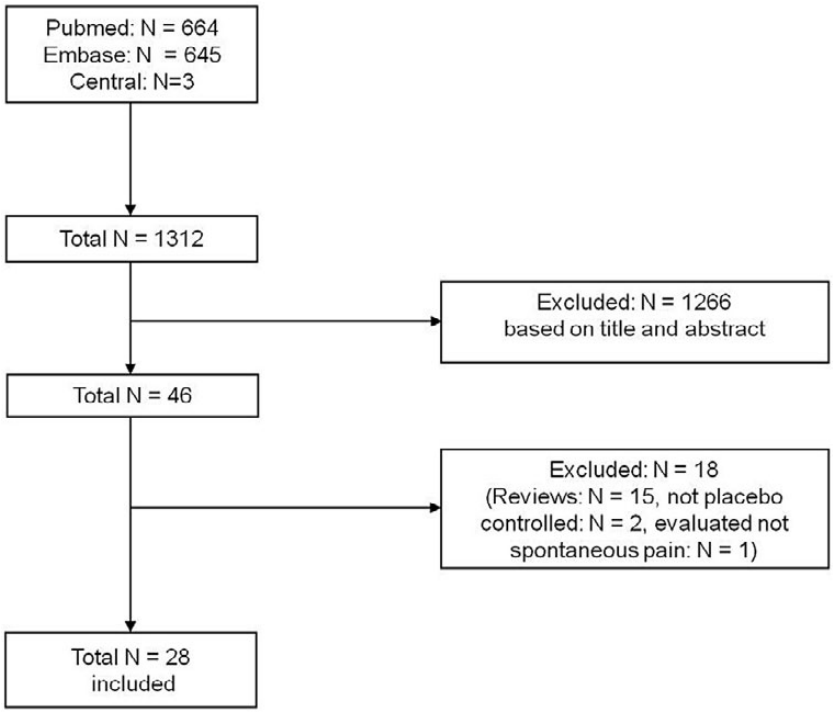

Figure 1 Flow chart of study selection.

Table 1 Included studies

Authors	QS	N	Patients	Interventions	Appl	Design	Primary outcome	Results	Individual effect size (inverse variance)
Max et al. 1995	7	7	Posttraumatic pain and allodynia	Ketamine: 2 h, 0.75 mg/kg/h	IV	Crossover	VAS pain after 2 hours	Ketamine significantly reduced background pain, p = 0.01	–0.88 [–1.98, 0.22]
Felsby et al. 1995a	8	10	Chronic neuropathic pain (after amputation (n = 3), after operation (n = 5), after radiation (n = 2))	Ketamine: 10 min, 0.2 mg/kg and 50 min, 0.3 mg/kg/h	IV	Crossover	VAS pain 15 min after infusion	Ketamine significantly reduced pain intensity, p = 0.006	–0.42 [–1.41, 0.45]
Felsby et al. 1995b	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	MgCl2 significantly reduced pain intensity, p = 0.084	–0.29 [–1.22, 0.64]
Nickolajsen et al. 1996	8	11	Post amputation stump and phantom limb pain	Ketamine: bolus 0.1 mg/kg/5 min and 7 μgr/kg/min for 40 min	IV	Crossover	VAS pain after infusion	Ketamine significantly reduced stump and phantom pain, p < 0.05*	–0.89 [–1.78, 0.01]
Eisenberg et al. 1998	10	20	Postherptic neuralgia	Memantine: wk 1:10 mg/d, wk 2/5: 20 mg/d	Oral	Parallel	VAS (0–10) pain after 5 weeks	No statistically significant difference in reduction of pain	0.23 [–0.65, 1.11]
Pud et al. 1998	7	13	Surgical neuropathic pain in cancer patients	Amantadine: 200 mg in 3 hours	IV	Crossover	VAS pain after 3 h infusions	Amantadine significantly reduced pain, p = 0.0001	–1.46 [–2.32, –0.60]
Medrik-Goldberg et al. 1999	9	30	Sciatica	Amantadine: 2.5 mg/kg in 2 hours	IV	Crossover	VAS pain after 180 min	No statistically significant difference in reduction of spontaneous pain	0.04 [–0.47, 0.55]
Galer et al. 2000a	9	22	Peripheral neuropathic pain (postherptic neuralgia (n = 13), diabetic polyneuropathy (n = 1), peripheral neuropathy other than diabetic (n = 8))	Riluzole: 100 mg/d for 2 weeks	Oral	Crossover	VAS pain after 2 weeks	No statistically significant difference in alleviating peripheral neuropathic pain, p > 0.10	0.26 [–0.34, 0.86]

Table 1 Continued

Authors	QS	N	Patients	Interventions	Appl	Design	Primary outcome	Results	Individual effect size (inverse variance)
Galer et al. 2000b	9	21	Peripheral neuropathic pain (postherptic neuralgia (n = 9), diabetic polyneuropathy (n = 1), peripheral neuropathy other than diabetic (n = 11))	Riluzole: 200 mg/d for 2 weeks	Oral	Crossover	VAS pain after 2 weeks	No statistically significant difference in in alleviating peripheral neuropathic pain, $p > 0.10$	–0.07 [–0.68, 0.54]
Gilron et al. 2000	8	16	Facial neuralgias (possible trigeminal neuropathy (n = 10), anaesthesia dolorosa (n = 4), idiopathic trigeminal neuralgia (n = 2))	Dextromethorphan: 120 mg/d, titrated to max 920 mg/d for 6 weeks	Oral	Crossover	VAS overall daily pain after 6 weeks	No statistically significant difference in reducing pain, $p = 0.81$	0.05 [–0.64, 0.74]
Nickolajsen et al. 2000	7	15	Neuropathic pain after amputation (n = 12) or operation (n = 3)	Memantine: wk 1: 5 mg/d, wk 2: 10 mg/d, wk 3: 15 mg/d, wk4/5: 20 mg/d	Oral	Crossover	VAS (0–10) pain during wk4/5	No significant difference in reducing spontaneous pain	–0.41 [–1.14, 0.32]
Leung et al. 2001	7	12	Neuropathic pain (postherptic neuralgia (n = 4), CRPS (n = 7), spinal cord injury (n = 1))	Ketamine: target plasma levels of 50, 100 and 150 ng/ml	IV	Crossover	VAS pain at 3 plasma levels	No significant reduction in spontaneous pain*	0.28 [–0.52, 1.08]
Abraham et al. 2002a	8	3	Phantom pain in cancer amputees	Dextromethorphan: 1 wk 120 mg/d	Oral	Crossover	VAS pain after 1 week	Dextromethorphan significantly reduced post amputation phantom limb pain, $p < 0.05$*	–2.27 [–4.42, –0.12]
Abraham et al. 2002b	8	3	Phantom pain in cancer amputees	Dextromethorphan: 1 wk 180 mg/d	Oral	Crossover	VAS pain after 1 week	Dextromethorphan significantly reduced post amputation phantom limb pain, $p < 0.05$*	–2.27 [–4.42, –0.12]

Brill et al. 2002	9	7	Postherptic neuralgia	MgSO4: 30 mg/kg MgSO4 in 30 min	IV	Crossover	VAS pain after 30 minutes	MgSO4 significantly reduced postherptic neuralgia pain, $p = 0.016$*	–1.50 [–2.68, –0.36]
Furuhashi-Yonaha et al. 2002	2	8	(CRPS (n = 4), visceral pain (n = 2), postherptic neuralgia (n = 1), phantom limb pain (n = 1))	Ketamine: 0.5 mg/kg every six hours for a week	Oral	Crossover	VAS pain after 1 week	Oral ketamine significantly reduced severity of the pain, $p < 0.05$	–1.57 [–2.68, –0.44]
Sang et al. 2002a	8	19	Diabetic neuropathy	Dextromethorphan: 7 wk titration until max tolerated doses and 2 wk maintenance, median doses 400 mg/d	Oral	Crossover	Gracely Box Scale during last week of treatment period	No significant difference in reducing pain	–0.41 [–1.05, 0.23]
Sang et al. 2002b	8	17	Postherptic neuralgia	Dextromethorphan: 7 wk titration until max tolerated doses and 2 wk maintenance, median doses 400 mg/d	Oral	Crossover	Gracely Box Scale during last week of treatment period	No significant difference in reducing pain	–0.03 [–0.70, 0.64]
Sang et al. 2002c	8	19	Diabetic neuropathy	Memantine: 7 wk titration until max tolerated doses and 2 wk maintenance, median doses 55 mg/d	Oral	Crossover	Gracely Box Scale during last treatment week	No significant difference in reducing pain	–0.04 [–0.68, 0.60]
Sang et al. 2002d	8	17	Postherptic neuralgia	Memantine: 7 wk titration until max tolerated doses and 2 wk maintenance, median doses 55 mg/d	Oral	Crossover	Gracely Box Scale during last week of treatment period	No significant difference in reducing pain	0.08 [–0.75, 0.59]
Wallace et al. 2002	7	62	Neuropathic pain (postherptic 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 difference in reducing spontaneous pain, $p = 0.613$*	0.11 [–0.39, 0.61]
Abraham et al. 2003a	6	10	Phantom pain in cancer (n = 8) and non cancer (n = 2) amputees	Dextromethorphan: 10 days 120 mg/d	Oral	Crossover	VAS pain after 10 days	All patients reported a >50% decrease in pain intensity after treatment	Not estimable**

Table 1 Continued

Authors	QS	N	Patients	Interventions	Appl	Design	Primary outcome	Results	Individual effect size (inverse variance)
Abraham et al. 2003b	6	10	Phantom pain in cancer (n = 8) and non cancer (n = 2) amputees	Dextromethorphan: 10 days 180 mg/d	Oral	Crossover	VAS pain after 10 days	All patients reported a >50% decrease in pain intensity after treatment	Not estimable**
Amin et al. 2003	8	17	Diabetic peripheral neuropathy	Amantadine: 1 × 200 mg in 500 ml 0.9% NaCl	IV	Crossover	VAS pain after 1 week	Amantadine significantly reduced pain intensity p = 0.003	–0.98 [–1.71, –0.25]
Jorum et al. 2003	7	12	Post traumatic neuralgia (n = 11) and postherptic neuralgia (n = 1)	Ketamine: bolus 60 μgr/kg and 6 μgr/kg for 20 min	IV	Crossover	VAS pain after infusion	ketamine significantly reduced spontaneous pain p = 0.015*	–1.08 [–1.94, –0.22]
Maier et al. 2003	11	16	Chronic phantom limb pain after amputation of arm or leg	Memantine: week 1 titration 30 mg/d: 5 mg/d + added 5 mg daily, w2+3: 30 mg/d	Oral	Crossover	VAS pain after 3 weeks	No significant difference in reducing phantom limb pain*	0.24 [–0.46, 0.94]
Carlsson et al. 2004	7	13	Neuropathic pain of traumatic origin	Dextromethorphan: 1× 270 mg	Oral	Crossover	VAS pain after 0–4 hours	Dextromethorphan significantly reduced pain, p < 0.05	–0.81 [–1.61, –0.01]
Wiech et al. 2004	8	8	Chronic phantom limb pain	Memantine: wk 1: 10 mg/d, wk 2: 20 mg/d, wk 3/4: 30 mg/d	Oral	Crossover	VAS pain after 4 weeks treatment	No significant difference in reducing intensity of chronic limb pain, p = 0.16*	0.74 [–0.27, 1.05]
Gottrup et al. 2006	8	19	Verified nerve injury pain	Ketamine: bolus 0.1 mg/kg in 10 min and 0.007 mg/kgmin in 20 min	IV	Crossover	VAS pain during infusion	Ketamine significantly reduced spontaneous pain, p < 0.01	–0.35 [–0.99, 0.29]
Schifitto et al. 2006	3	45	HIV associated sensory neuropathy	Memantine: wk 1: 10 mg/d + added weekly for 4 wk 10 mg/d, wk 4/16: 40 mg/d	Oral	Parallel	VAS pain after 16 weeks	No significant difference in reducing HIV associated sensory neuropathy, p = 0.87*	0.05 [–0.54, 0.64]
Forst et al. 2007a	10	12	Neuropathic pain (postherptic pain (n = 3), posttraumatic injury (n = 6), CRPS (n = 3))	Novel glutamate antagonist CNS 5161 HCl: single dose of 125 μgr	Oral	Crossover	VAS pain after 12 hours	No significant difference in reducing pain	0.16 [–0.64, 0.96]

Forst et al. 2007b	10	12	Neuropathic pain (postherptic pain (n = 2), diabetic neuropathy (n = 3), posttraumatic injury (n = 6), CRPS (n = 1))	Novel glutamate antagonist CNS 5161 HCl: single dose of 250 μgr	Oral	Crossover	VAS pain after 12 hours	No significant difference in reducing pain	0.30 [–0.51, 1.11]
Forst et al. 2007c	10	14	Neuropathic pain (diabetic neuropathy (n = 8), posttraumatic injury (n = 4), CRPS (n = 2))	Novel glutamate antagonist CNS 5161 HCl: single dose of 500 μgr	Oral	Crossover	VAS pain after 12 hours	No significant difference in reducing pain, p = 0.11	–0.40 [–1.15, 0.35]
Eichenberger et al. 2008	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 60 min after infusion	Ketamine significantly reduced phantom limb pain, p < 0.001*	–1.75 [–2.06, –0.72]
Schwartzman et al. 2009	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, p < 0.05	–0.55 [–1.00, 0.09]
Sigtermans et al. 2009	8	60	CRPS	Ketamine (S+): 22.2 ± 2.0 mg/h (mean ± SD) continuously during 4.2 days	IV	Parallel	VAS pain after 1 week	Ketamine significantly reduced spontaneous pain, p < 0.001	–5.59 [–6.76, –4.47]
Finch et al. 2009	7	20	CRPS	Ketamine 10% cream	Topical	Crossover	VAS pain after 30 min	No significant difference in reducing pain	0.00 [–0.20, 0.20]

QS: quality score. Appl: 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.

Table 2 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, light-headedness, 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, light-headedness, 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.
MgSO4	Mild feeling of warmth at the site of infusion.
MgCl2	Heat sensations, injection pain and sedation.
Riluzole	Not mentioned.

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 summarize 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

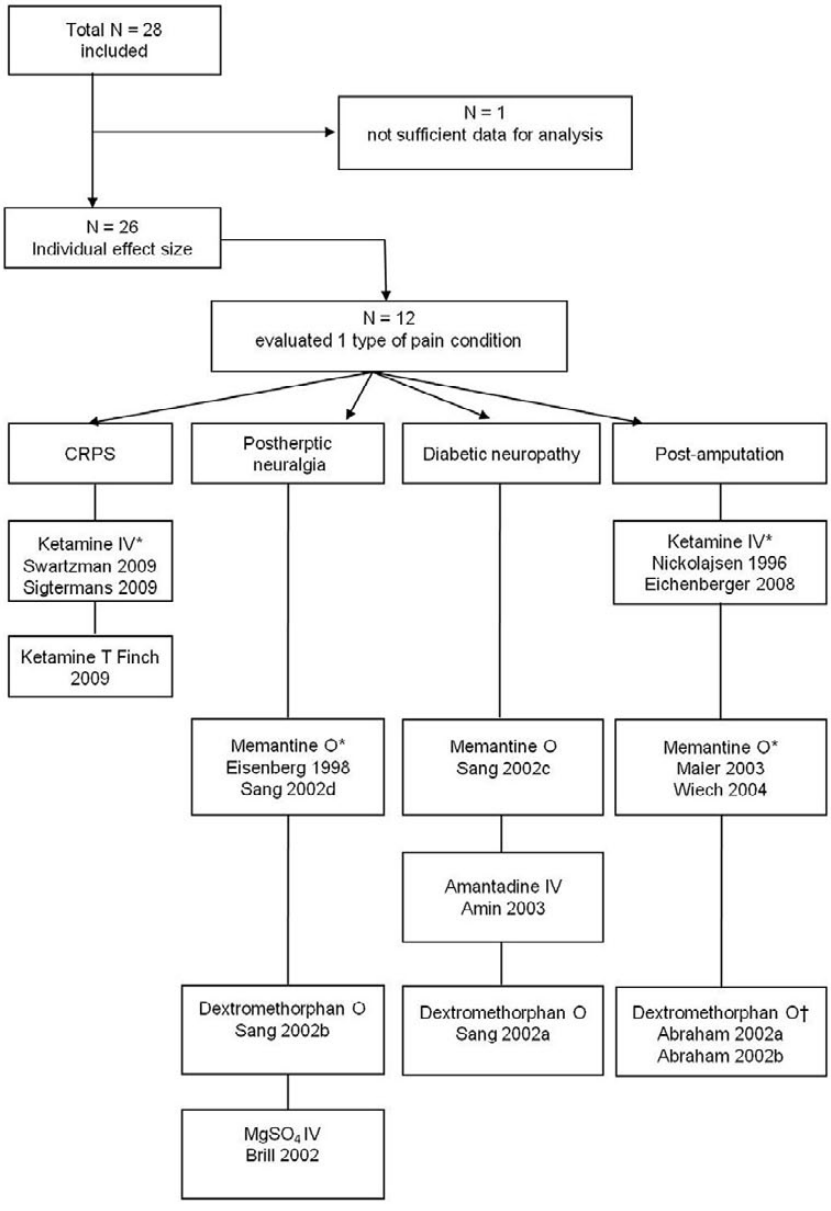

Figure 2 Included studies divided in four pain patients groups. *Summarize effect size was calculated for minimal two studies evaluating the same intervention and route of administration in the same pain patient group. †Results of the trials were not summarized, because trials were performed and reported within the same study. IV = intravenous; O = oral; T = topical.

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

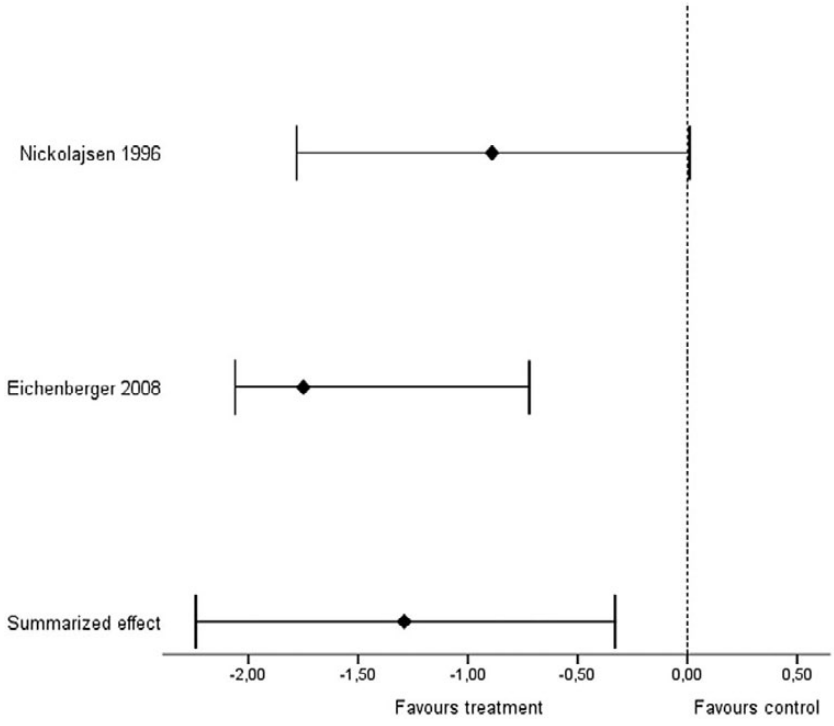

Figure 3 Intravenous ketamine versus placebo in postamputation pain. $I^2 = 0\%$. Pooled summarized effect size, fixed effect model: –1.18 (confidence interval 95% –1.98, –0.37), $P = 0.004$.

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.

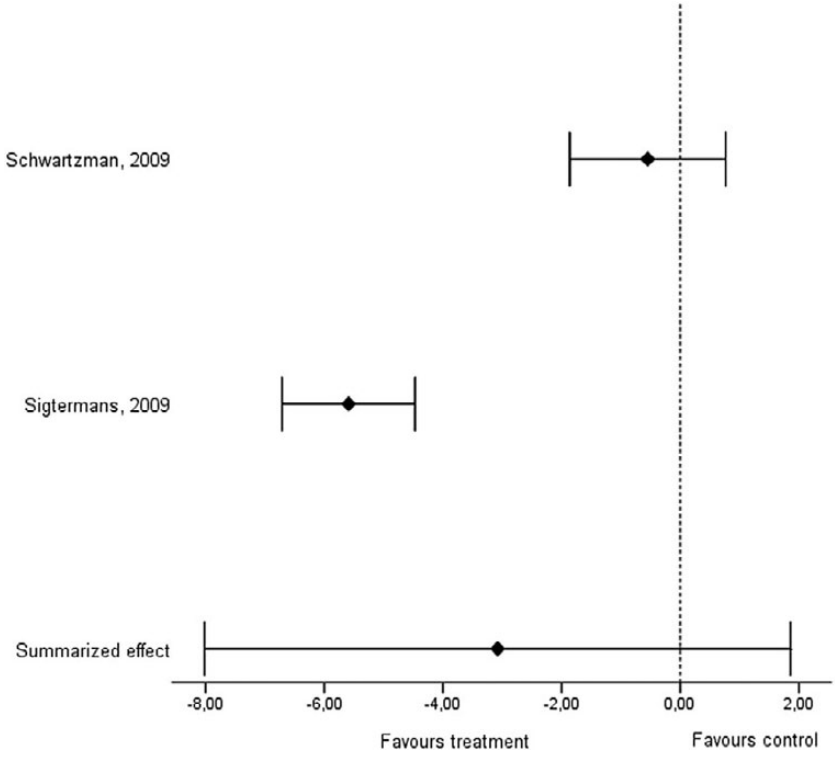

Figure 4 Intravenous and topical ketamine versus placebo in CRPS. $I^2 = 55\%$. Pooled summarized effect size, random effect model: –0.65 (confidence interval 95% –1.47, 0.16), $P = 0.11$.

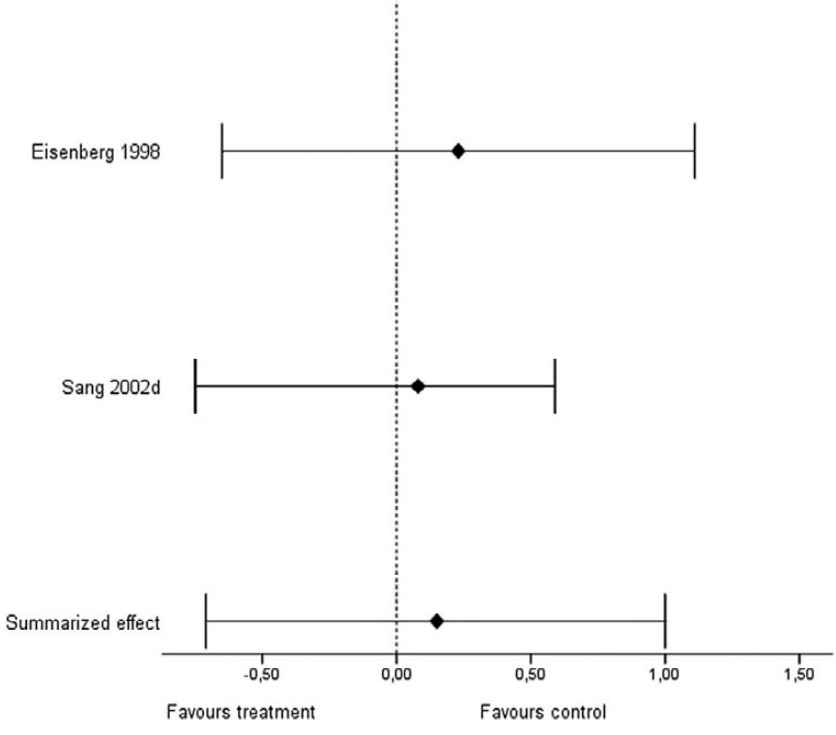

Figure 5 Oral memantine versus placebo in postherptic neuralgia. $I^2 = 0\%$. Pooled summarized effect size, fixed effect model: 0.03 (confidence interval 95% –0.51, 0.56), $P = 0.92$.

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

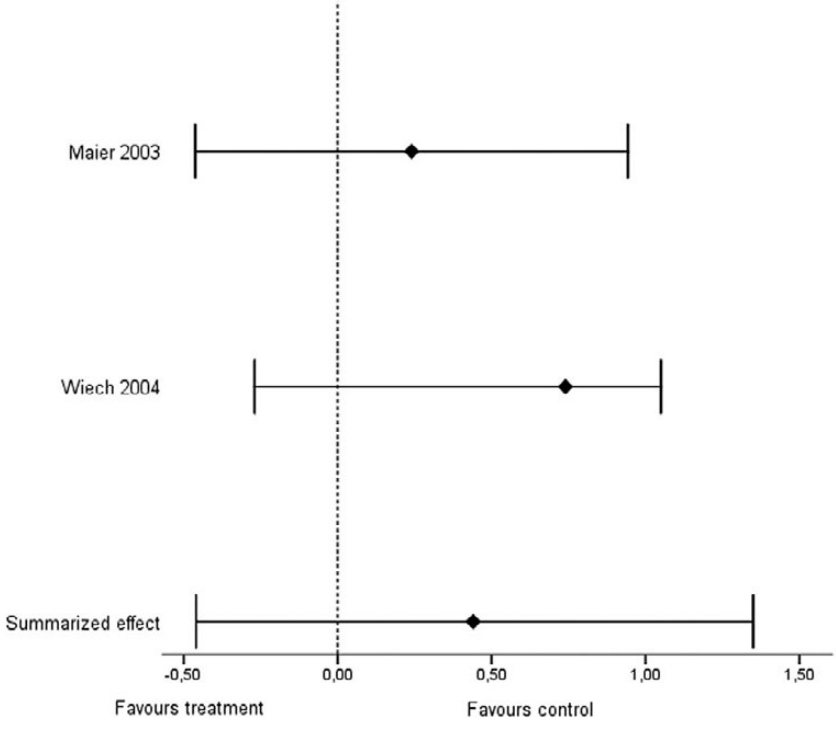

Figure 6 Oral memantine versus placebo in postamputation pain. $I^2 = 0\%$. Pooled summarized effect size, fixed effect model: 0.38 (confidence interval 95% –0.21, 0.98), $P = 0.21$.

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 subunit 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 hypersensitivities 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(+) eantiomer 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 yet be made about the efficacy of NMDA

receptor antagonists on neuropathic pain. However, evidence 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.

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Appendix [15,16,18,60–63]

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

$$g_i = (M_e - M_c)/\text{SD pooled}$$

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

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

$$g_i = t\sqrt{(n_e + n_c)}/\sqrt{(n_e n_c)}, \text{ and when } n_e \text{ and } n_c \text{ are equal } g_i = 2t/\sqrt{N}$$

Where, t = value of the *t*-test, N = total sample size.

Calculating Hedges' g_i 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_i can be calculated (see above).

Calculating 95% Confidence Intervals (CI) for Hedges' g_i

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

$$V_i = (N/n_e n_c) + (g_i^2/2N)$$

Where Vi = within-study variance of individual effect size i.

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

$$g_s = \sum g_i W_i / \sum W_i$$

$$Wi = 1/V_i$$

Where, g_s = summarized hedges' g, Wi = estimated weight for individual study i.

Calculating Homogeneity Statistics I^2

I^2 = proportion of total variability explained by heterogeneity

$I^2 = (Q - (k-1))/Q \times 100\%$, for $Q > (k-1)$

$I^2 = 0$, for $Q \le (k-1)$

$$Q = \sum W_i g_i^2 - \left(\sum W_i g_i\right)^2 / \sum W_i$$

Q = Q 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

$$g_s = \sum g_i W_i / \sum W_i$$

$$Wi = 1/V_i^*$$

$$V_i^* = \sigma_\theta^2 + V_i,$$

$$\sigma_\theta^2 = (Q - (k-1))/c,$$

$$c = \sum W_i - \left(\left(\sum W_i^2\right)/\sum W_i\right)$$

Where Vi* = total variance, σ_θ^2 = between study variance, Q = Q statistics, k = number of studies in the meta-analysis.

Calculating 95% CI for g_s

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

$$V_s = 1/\sum W_i$$

Where, V_s = variance of summarized effect size.

Calculating P*-Values for g_s*

$$Z = |g_s|/\sqrt{V_s}$$

Where, Z = *Z*-value.

P vales can be obtained using Z table.

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