Open Journal of Dentistry and Oral Medicine 5(4): 59-71, 2017 http://www.hrpub.org
DOI: 10.13189/ojdom.2017.050401

NMDA Receptor Antagonists for the Treatment of Neuropathic Pain Compared to Placebo: A Systematic Review and Meta-analysis

Byron Larsen[1], Kristin Mau[1], Mariela Padilla[2], Reyes Enciso[3,*]

[1]Master of Science Program in Orofacial Pain and Oral Medicine, Herman Ostrow School of Dentistry, University of Southern California, USA
[2]Division of Periodontology, Diagnostic Sciences and Dental Hygiene, Herman Ostrow School of Dentistry, University of Southern California, USA
[3]Division of Dental Public Health and Pediatric Dentistry, Herman Ostrow School of Dentistry, University of Southern California, USA

Abstract The objective of this study is to evaluate the efficacy of N-Methyl-D-aspartate (NMDA) receptor antagonists on neuropathic pain disorders that can occur in the orofacial region. These disorders included: Postherpetic Neuralgia (PHN), Complex Regional Pain Syndrome (CRPS), Atypical Odontalgia, Temporomandibular Joint (TMJ) Arthralgia and facial neuropathies. **Materials and Methods:** Three databases (Medline through PubMed, Web of Science, and Cochrane library) were searched on January 25, 2017 for randomized placebo-controlled studies using a NMDA receptor antagonist to treat spontaneously occurring neuropathic pains as compared to placebo. Two review authors separately evaluated the risk of bias. **Results:** The initial search yielded 267 unduplicated references, of which only 16 were eligible for inclusion. Six of these studies had an unclear risk of bias and ten had a high risk of bias. Four studies were included for meta-analysis. Oral memantine was found not to be more effective than placebo in treating PHN ($p=0.735$), while oral and IV ketamine were more effective than placebo in treating CRPS ($p<.001$). **Conclusions:** The quality of the evidence favorable to the use of ketamine in the treatment of CRPS is low. Inconclusive evidence in favor of other NMDA antagonist receptors was found. Additional studies with lower risk of bias and larger sample sizes are needed in this area of study.

Keywords N-methyl-D-aspartate (NMDA) Receptor Antagonist, Ketamine, Post-Herpetic Neuralgia (PHN), Complex Regional Pain Syndrome (CRPS), Facial Neuropathies

1. Introduction

Neuropathic pain has been linked to structural and functional somatosensory nervous system alternations that produce spontaneous pain and pathologically intensified reactions to noxious and innocuous stimuli [1]. It is suggested that different mechanisms are at play regarding orofacial neuropathic pain due to the diverse clinical manifestations in disorders of various etiologies [2]. More specifically, involvement pertains to both peripheral and central sensitization mechanisms [3]. Campbell and Meyer [2] explain that altered responses can result from either injured axons or intact nociceptors that are in the proximity of the injured nerve. They additionally proposed that these mechanisms may be observed in pharmacological treatment outcomes [2].

N-methyl-D-aspartate (NMDA) receptors are involved in maintaining neural hyper excitability, including central sensitization [4]. Prolonged activation of nociceptors in the case of neuropathic pain comes from ectopic discharge generated in injured nerves or ganglia, which results in a continuous release of glutamate, that can lead to longer-lasting membrane depolarization [4]. It is the prolonged firing of C-fiber nociceptors that releases glutamate, which in turn acts on NMDA receptors causing central and peripheral sensitization. Clinically, this extended membrane depolarization presents as spontaneous pain, hyperalgesia and allodynia [5]. Considering that the blockage of NMDA receptors may disrupt or even overturn the pain process, NMDA receptor antagonists are being proposed in the pharmacological treatment of neuropathic pain [6]. Therefore, blocking these receptors with antagonist drugs can reduce the symptoms of hyperalgesia, allodynia and spontaneous pain [4, 6].

Neuropathic pain disorders can occur in the orofacial region including: Postherpetic Neuralgia (PHN), Complex Regional Pain Syndrome (CRPS), Atypical Odontalgia,

Temporomandibular Joint (TMJ) Arthralgia and facial neuropathies. The current choice of treatments for chronic pain, particularly neuropathic pain (i.e. that associated with peripheral nerve or CNS pathology) is very limited and the use of current medications such as tricyclic antidepressants (TCAs) and neuromodulators only show partial efficacy in the majority of patients [7]. According to Coluzzi and Mattia [8], "TCAs have become the mainstay in the treatment of neuropathic pain."

Since antagonists to NMDA receptors have been suggested to play a major role in the treatment of neuropathic pain [4, 6, 7], the objective of this review is to perform a meta-analysis evaluating the effects of individual NMDA receptor antagonists on patients with varying conditions affecting the orofacial region of the body.

2. Materials and Methods

2.1. Criteria for Considering Studies for this Review

Included studies were limited to randomized controlled trials on the efficacy of NMDA receptor antagonists compared to placebo group in adult patients to reduce spontaneous pain. Studies included at least one clinical endpoint on spontaneous pain in patients with postherpetic neuralgia (PHN), CRPS, facial neuropathy, atypical odontalgia and TMJ arthralgia. Two reviewers individually assessed trial reports to determine eligibility. Editorials/commentaries, reviews, case studies, animal studies, cost-effectiveness studies, pharmacokinetic studies, and guidelines were omitted. Articles not available in English were also omitted. Not randomized studies or uncontrolled studies, as well as open label studies were rejected. All studies where pain was induced or non-spontaneous were excluded. The primary outcome was the difference in pain relief between experimental and placebo conditions as measured on a numerical rating scale (NRS) or visual analog scale (VAS).

2.2. Search Strategy

For the identification of studies included or considered for this review, the following electronic databases were searched.

MEDLINE via PubMed (searched on 2/14/2017). PubMed Search Strategy:

("Ketamine"[Mesh] OR ketamine OR "NMDA" OR "Receptors, N-Methyl-D-Aspartate"[Mesh] OR "Amantadine"[Mesh] OR "amantadine" OR "Memantine"[Mesh] OR "memantine" OR "Riluzole"[Mesh] OR "Riluzole" OR "Dextromethorphan" OR "Dextromethorphan"[Mesh]) AND (post-herpetic OR postherpetic OR "Neuralgia, Postherpetic"[Mesh] OR "Complex Regional Pain Syndromes"[Mesh] OR CRPS OR (Complex regional pain syndrome) OR "Temporomandibular Joint Disorders"[Mesh] OR "Temporomandibular Joint Dysfunction Syndrome"[Mesh] OR TMJ OR TMD OR (temporomandibular joint) OR (temporomandibular disorder) OR temporo-mandibular OR BMS OR (burning mouth syndrome) OR "Burning Mouth Syndrome"[Mesh] OR arthralgia OR "Arthralgia"[Mesh] OR myofascial OR "Myofascial Pain Syndromes"[Mesh]). Filters: Language, limit to English; Species, limit to humans.

The Web of Science (searched on 2/14/2017).

TOPIC: ketamine OR NMDA OR Receptors, N-Methyl-D-Aspartate OR amantadine OR memantine OR Riluzole OR Dextromethorphan AND TOPIC: post-herpetic OR postherpetic OR Neuralgia, Postherpetic OR Complex Regional Pain Syndromes OR CRPS OR Complex regional pain syndrome OR Temporomandibular Joint Disorders OR Temporomandibular Joint Dysfunction Syndrome OR TMJ OR TMD OR temporomandibular joint OR temporomandibular disorder OR temporo-mandibular OR BMS OR burning mouth syndrome OR arthralgia OR myofascial OR Myofascial Pain Syndromes AND TOPIC: random OR randomized OR randomly.

The Cochrane Library (searched on 2/14/17):

(ketamine OR NMDA OR Receptors, N-Methyl-D-Aspartate OR amantadine OR memantine OR Riluzole OR Dextromethorphan) AND (post-herpetic OR postherpetic OR Neuralgia, Postherpetic OR Complex Regional Pain Syndromes OR CRPS OR Complex regional pain syndrome OR Temporomandibular Joint Disorders OR Temporomandibular Joint Dysfunction Syndrome OR TMJ OR TMD OR temporomandibular joint OR temporomandibular disorder OR temporo-mandibular OR BMS OR burning mouth syndrome OR arthralgia OR myofascial OR Myofascial Pain Syndromes) AND (random OR randomized OR randomly).

Reviews, included studies and clinical guidelines were scanned for relevant trials.

2.3. Data Collection and Analysis

Studies were limited to adults participating in randomized controlled trials on the efficacy of NMDA receptor antagonists on spontaneous neuropathic compared to placebo. Only studies in English were included. Two reviewers individually assessed abstracts to determine eligibility. If neuropathic pain was induced and not naturally occurring these studies were excluded from search results. Two authors (B.L and K.M.) independently screened the titles and abstracts resulting from the search strategy. If the abstracts met the inclusion criteria the same two authors reviewed the full text of the articles. The third author (R.E.) resolved all disagreements as to whether a study was included or excluded. This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)

statement [9].

Two reviewers (B.L. and K.M.) extracted the methods, participants, treatment groups and interventions, comparison groups, demographics and outcomes from the full-text articles eligible for inclusion.

2.4. Assessment of Risk of Bias in Included Studies

The risk of bias tool, described in the Cochrane Handbook for Systematic Reviews of Interventions [10], was used to assess each eligible study for risk of bias. Two reviewers (B.L and K.M.) assessed risk of bias for each included study. Risk of bias was assessed in the following categories: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, other potential bias and overall risk of bias.

2.5. Measures of Treatment Effect

The primary endpoint for the studies was measuring the efficacy of the NMDA receptor antagonists in reducing pain scores of the subjects compared to placebo. Reduction in pain intensity was measured in multiple different ways throughout the studies by the different authors. The different measurement methods included: VAS 0-10, VAS 0-100, numerical verbal scale 0-10, NPS 0-10, M-VAS, 11 p0oint NRS-PI, 5 point categorical scales, VAS-PR 0-100, NRS 0-10 and 20 point Gracely Box Scale. To measure the treatment effect by using different scales, standardized mean difference (SMD) with 95% confidence intervals (CI) was used. Quality of evidence assessment, and summary of the findings, were conducted using the software GRADE profiler (GRADEpro), following the Cochrane Collaboration and GRADE Working Group.

3. Results

3.1. Results of the Search

The initial search strategy yielded 320 references with 260 unduplicated plus seven hand-search references. Independent assessment by two review authors based on the abstracts and titles reduced the number of relevant manuscripts to 29. Main reasons for exclusion of those references were that the study was a review or a systematic review (n=70), not in English (n=3 in German), animal study (n=5), in children (n=2), evidence-based recommendations (n=1), book chapter (n=1), editorial/opinion letter (n=18), only abstract (n=1), pilot study (n=1), open-label study (n=3), not a RCT (n=9), different condition (n=78), different intervention (n=46).

All 29 eligible manuscripts identified were searched for full-text and analyzed for inclusion independently by two review authors, from these, 16 manuscripts were found relevant for inclusion. Main reasons for 13 excluded references were that the intervention under study was not a NMDA (n=2), different conditions (n=2), a review of the literature (n=1), abstract proceedings (n=2), not a RCT (n=4), pilot study (n=1) and an open label study (n=1). PRISMA flowchart shows a summary of our search results (Figure 1).

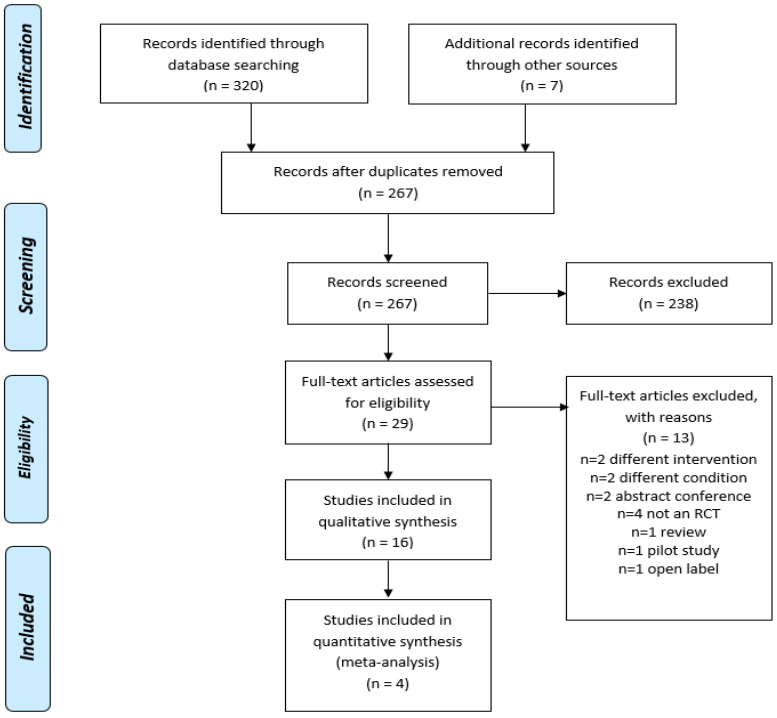

Figure 1. PRISMA flow diagram.

3.2. Included Studies

There were sixteen included studies utilized for qualitative analysis [11–26] listed in Table 1. These studies were limited to randomized controlled trials on the efficacy of NMDA receptor antagonists compared to placebo groups in adult patients with varying conditions to reduce spontaneous pain. Each study additionally included at least one clinical endpoint on spontaneous pain. Ten of the sixteen studies were crossover as well [11, 13, 14, 16–20, 22, 23]. The number of participants ranged from 8 in one of the studies [14] up to 92 in another study [17]. Regarding the ages of the participants, the range was anywhere from 20 years old to 93 years old. All studies included adult males and females. The neuropathic pain conditions included were CRPS, PHN, TMJ arthralgia, atypical odontalgia, and facial neuropathies. Inclusion and exclusion criteria for the different studies varied pertaining mostly to the criteria defining the different condition diagnosis (Table 1).

Of the 16 studies, 10 studies used Ketamine as the intervention and 3 of these studies used the S enantiomer of Ketamine while the others used the racemic (R/S) Ketamine form. Of the remaining studies 1 used Memantine, 1 used Riluzole, 3 used Dextromorphan and one studied Dextromorphan and Memantine. The NMDA receptor antagonists have different affinities for the receptor and as such have varying effects on pain. Additionally, the interventions had different routes of administration, 6 studies gave the subjects the intervention intravenously, 6 were given the drugs orally in the form of a capsule or syrup and 3 were applied in a topical cream. The Ayesh et al. [11] study examined the effects on NMDA receptor antagonists on TMJ arthralgia, they were the only study to use intra-articular injection as the route of administration for the NMDA receptor antagonist.

Table 1. Characteristics of included RCT studies

Reference	Year, Country, Study design	Patient's condition	Interventions and sample size	Age mean or range (years) Gender: M/F	Inclusion criteria
Ayesh et al. 2008[11]	2008, Denmark Crossover	TMJ Arthralgia patients	N=36 • Intra-articular ketamine (n=18) • Saline (n=18 randomized; n=16 completed)	Age range: 20-39 3M/15F	TMJ arthralgia according to Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)
Baad-Hansen et al. 2007[12]	2007, Denmark Crossover	Atypical odontalgia	Crossover N=14 randomized; 10 completed • S-ketamine • Fentanyl • Isotonic NaCl	I: 48.1 y.o. 3M/7F C: 40.6 y.o. 4M/6F	(1) Atypical odontalgia pain (>6 months); (2) Non-paroxysmal pain present during most of the day; (3) No tissue pathology.
de Barros et al. 2012[13]	2012, Brazil Crossover	PHN	N=12 total • 1% topical S-ketamine (n=6) • Placebo (n=6)	71.7 4M/8F	1) Older than 18 using amitriptyline and gabapentin to control PHN pain for at least 1 month; 2) Persistent pain at herpes zoster site for 30 days post skin healing
Eide et al. 1994[14]	1994, Norway Crossover	PHN	Crossover: N = 8 patients • Ketamine hydrochloride • Morphine hydrochloride • Saline	71.8 4M/4F	PHN patients
Eisenberg et al., 1998[15]	1998, Israel RCT	PHN	N = 24 • Oral memantine (n=12) • Oral placebo (n=12)	I: 65.7 5M/7F C: 70.8 7M/5F	Symptoms and physical findings consistent with PHN
Finch et al. 2009[16]	2009, Australia, Crossover	CRPS	Crossover N= 20 • Racemic ketamine hydrochloride 10% in PLO • Placebo	39.8 6M/14F	Diagnostic criteria for CRPS
Galer et al. 2000[17]	2000, United States Crossover	DN, PHN, Peripheral Neuropathy	**Total N = 43**	Study 1: 66 y.o. 12M/10F	1) >18 years old; 2) diagnosis of chronic peripheral neuropathic pain due to

			Crossover Study1: (1)100mg/day Riluzole (n=22) (2) placebo (n=22) **Crossover Study2:** (1)200mg/day Riluzole (n=21) (2) placebo (n=21)	Study 2: 64 y.o. 13M/8F	peripheral neuropathy or focal peripheral nerve injury > 3 months.
Gilron et al. 2000[18]	2000, United States Crossover	Facial Pain/Possible Trigeminal Neuropathy, Anesthesia Dolorosa, Idiopathic TN	Crossover N= 19 • Dextromethorphan • Low-dose lorazepam	50.26 5M/14F	Age between 18 and 89 years; daily paroxysms or continuous pain for at least 3 months; a previous trial of carbamazepine or baclofen (for TN) or a tricyclic antidepressant, an opioid, or gabapentin (for other neuralgias);
Jørum et al. 2003[19]	2003, Norway Crossover	Post-Traumatic Neuralgia, PHN	Crossover N=12 • alfentanil bolus • ketamine bolus • NaCl	47.5 5M/7F	Clinical symptoms and findings of neuropathic pain following trauma (with special emphasis on severe cold allodynia and hyperalgesia.
Leung et al. 2001[20]	2001, United States Crossover	Post-Nerve Injury Neuropathic Pain including PHN	Crossover N=12 • ketamine IV • alfentanil IV • placebo (diphenhydramine IV)	55.8 7M/5F	Demonstration of allodynia plus medical history suggesting nerve injury
Lynch et al, 2005[21]	2005, Canada RCT	DN, PHN, Post-Surgical/Post-traumatic	• 2% amitriptyline (n = 22 but 3 withdrew) • 1% ketamine (n = 22 but 3 withdrew) • 2% amitriptyline and 1% ketamine (n=23 but 3 withdrew) • Placebo cream (n=25 but 3 withdrew)	I: 1) 24-76 9M/13F 2) 30-78 11M/11F 3) 25-82 12M/11F C: 34-84 15M/10F	Established diagnosis of PHN, diabetic neuropathy with moderate to severe pain persisting despite other Tx modalities for 3 months or longer with allodynia or hyperalgesia in the pain area
McQuay et al. 1994[22]	1994, United Kingdom Crossover	Post-Surgical Neuralgia, Post-stroke Pain, Brachial Plexus Avulsion, Phantom Limb Pain, PHN, DN	N=19 randomized; N=12 completed **Phase 1:** • Dextromethorphan 13.5mg, 3 x day • Placebo • Phase 2: • Dextromethorphan 27mg, 3 x day • Placebo	60.6 12M/7F	Male or female patients being treated for neuropathic pain, with a proven pathological process related to the painful area with demonstrable somatosensory dysfunction
Nelson et al. 1997[23]	1997, United States Crossover	DN, PHN	N=32 Crossover; N=26 completed • Dextromethorphan • Lactose placebo	DN: 54 10M/3F PHN: 65 11M/2F	Age of between 18 and 85 years; daily pain of at least moderate intensity > 3 months present more than 50% of the day; a previous trial of a tricyclic antidepressant medication.
Sang et al. 2002[24]	2002, United States RCT	DN, PHN	**D**N (n=23)/PHN (n=22) • Dextromethorphan and memantine • active placebo: 0.2 and 0.06 mg lorazepam	DN: 55 12M/11F PHN: 69 12M/10F	Adults > 18 y.o. with at least moderate pain for at least 50% of the day for a minimum of 3 months caused by either PHN or DN; previously failed trial of a tricyclic antidepressant for at least 2 weeks
Schwartzman	2009, United	CRPS	• Ketamine IV (n=9)	I: 24-47	Intractable CRPS > 6 months and

et al. 2009[25]	States RCT		• Saline (n=10)	0M/9F C: 27-60 1M/9F	failed at least 3 therapies: nerve blocks, opioid analgesics, non-opioid analgesics, non-steroidal anti-inflammatory drugs, anti-seizure medications, antidepressants, muscle relaxants or physical therapy.
Sigtermans et al. 2009[26]	2009, The Netherlands RCT	CRPS	• S(+)-ketamine (n=30) • Saline (n=30)	I: 43.7 8M/22F C: 47.5 4M/26F	CRPS-1 patients based on the International Association for the Study of Pain criteria.

Abbreviations: M/F: Male/female gender; TMJ: Temporo-mandibular joint; PHN: Post-herpetic neuralgia; DM: Diabetes mellitus; TN = Trigeminal Neuralgia; I=Intervention; C=control; y.o. = years old; PLO= Pluronic lecithin organogel.

Table 2. Summary of risk of bias for eligible RCT studies. Key: - Low risk, + high risk, ? unclear.

Study	Random Seq. Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other potential bias	*Overall Bias*
Ayesh et al. 2008[11]	?	_	?	_	_	_	?
Baad-Hansen et al. 2007[12]	_	_	?	+	_	?	+
de Barros et al. 2012[13]	?	?	?	_	_	+	+
Eide et al. 1994[14]	?	?	?	_	_	+	+
Eisenberg et al., 1998[15]	-	?	?	+	_	+	+
Finch et al. 2009[16]	?	_	_	_	_	_	?
Galer et al. 2000[17]	_	?	?	+	_	_	+
Gilron et al. 2000[18]	?	_	?	?	_	+	+
Jørum et al. 2003[19]	-	?	?	?	_	_	?
Leung et al. 2001[20]	?	_	?	?	_	?	?
Lynch et al. 2005[21]	-	_	?	_	_	+	+
McQuay et al. 1994[22]	_	_	?	+	_	+	+
Nelson et al. 1997[23]	_	?	?	+	_	+	+
Sang et al. 2002[24]	_	_	?	?	_	_	?
Schwartzman et al. 2009[25]	?	?	_	_	_	+	+
Sigtermans et al. 2009[26]	_	_	?	_	_	_	?

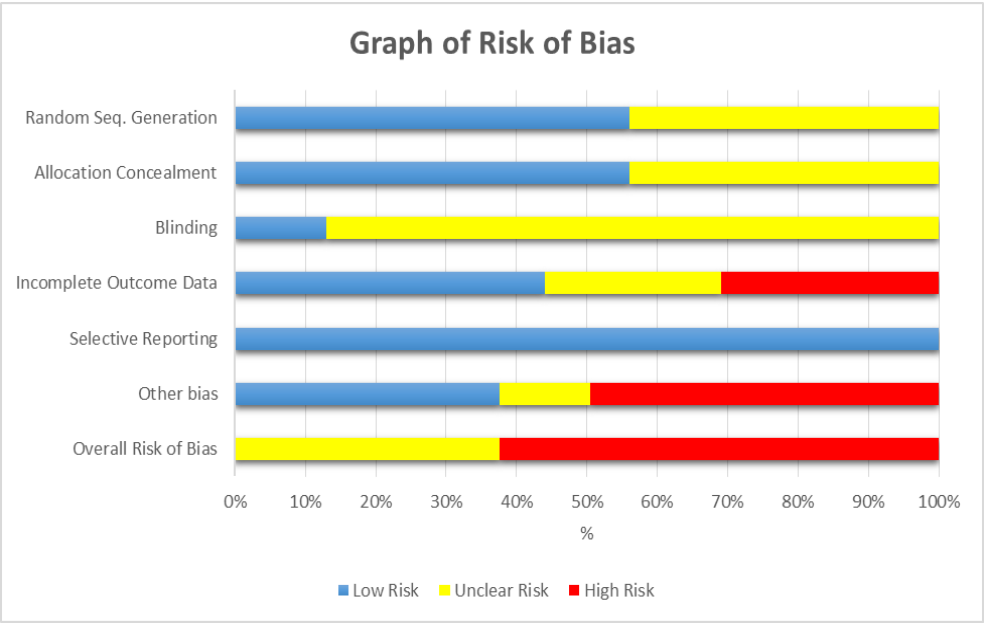

Figure 2. Summary of risk of bias for eligible RCT studies

3.3. Risk of Bias in Included Studies

A summary of the risk of bias table (Table 2) is presented in this review with an accompanying graph of the risk of bias (Figure 2).

Random sequence generation method was identified as low risk in 9 of 16 studies. These studies used offsite randomization, computer generated random sequencing or Latin square design [12, 15, 17, 19, 21–24, 26]. The remaining seven studies included were deemed at unclear risk of bias because the method of randomization was not clearly discussed [11, 13, 14, 16, 18, 20, 25].

Allocation concealment: A low risk of bias was determined to be present in 9 out of 16 studies. These studies had randomization codes provided in sealed envelopes and access to the randomization was not available [11, 12, 16, 18, 20–24, 26]. Seven studies had an unclear risk of bias. These studies were unclear as to how the concealment strategy occurred [13–15, 17, 19, 23, 25].

Blinding: Two of 16 studies were determined to be low risk of bias when evaluating the blinding. In these cases it was clearly stated that the participants, and all those involved in the participants care, were blinded [16, 25]. The 14 remaining included studies were deemed to have an unclear risk of bias. These studies failed to list if all the participants, investigators, outcome assessors and data analyst involved in the study were blinded to the randomization sequence [11–15, 17–24, 26].

Incomplete Outcome Data: Seven studies were considered low risk of bias because all participants were accounted for at the end of the study [11, 13, 14, 16, 21, 25, 26]. In the Ayesh et al. [11] and the Sigtermans et al. [26] studies, 2 participants dropped out but data analyses were completed on all participants in the study. Four studies were considered an unclear risk of bias [18–20, 24]. In the Gilron et al. [18] study, 3 out of 18 patients (15.8%) did not complete the study. Nine of the 45 patients didn't complete the Sang et al. [24] study, however this did not unbalance the groups and the reason for dropping out was mostly unrelated to treatment [24]. The Jørum et al. [19] study had no drop outs but during treatment 3 patients were given an extra 2 hours to 2 days to allow their levels of medication to return to baseline before the next treatment infusion. In the study by Leung et al. [20] there was no mention if all the patients or only a portion of the patients completed the study. Five studies were considered at high risk of bias [12, 15, 17, 22, 23] because 20% or more of the participants did not complete the study.

Selective Reporting: All of the pre-specified outcomes were reported in each study [11–26].

Other Potential Sources of Bias: Six studies had a low risk of bias because no significant differences between the subject groups were noted for any baseline or demographic variable [11, 14, 16, 17, 19, 24, 26]. Two studies had an unclear risk of bias [12, 20]. In the study by Baad-Hansen et al. [12], Pfizer Denmark donated the S -ketamine used in the study but no other funding was reported. In the Leung et al. [20] study an antihistamine was used as an active placebo. Eight studies had a high risk of bias due to the concurrent use of medications throughout the studies [13, 15, 18, 21–23, 25].

Overall Risk of Bias: Of the included studies, ten were determined to have a high risk of bias, while the remaining six included studies had an unclear risk of bias (Table 2; Figure 2).

3.4. Meta-analyses

PHN: Two studies comparing oral memantine to placebo in PHN patients reported baseline and post-treatment intensity of spontaneous pain [15, 24] and were included in the meta-analysis. There was no statistical heterogeneity (Q p= 0.800; I2 = 0%) and fixed effect model was used to report pooled results. The NMDA receptor antagonist was not statistically significant better than placebo in reducing pain intensity in PHN patients (SDM = -0.092; 95% CI = -0.627 to 0.442; p = .735) An overall negative standardized difference in means (SDM) represents a favorable result with a larger decrease in pain intensity in the NMDA group compared to the placebo group, however this difference was not statistically significant (Figure 3).

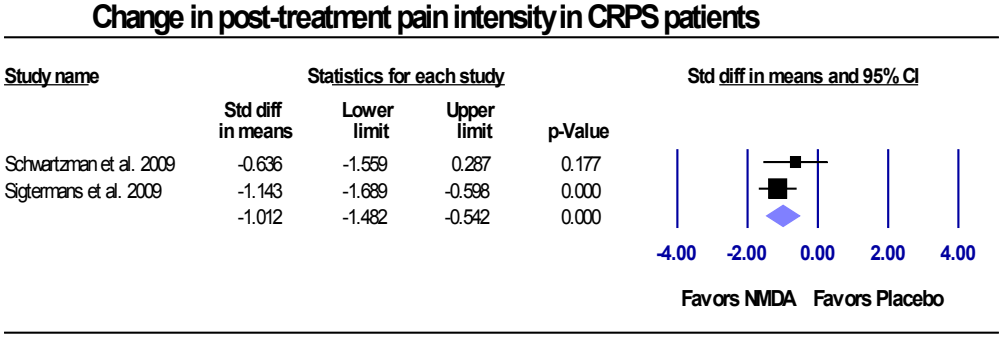

Figure 3. Oral memantine versus placebo in PHN patients.

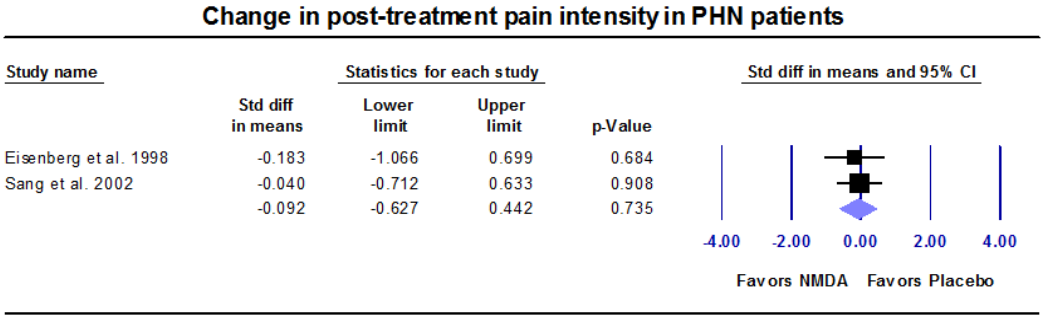

Figure 4. Ketamine versus placebo in CRPS patients

CRPS: Two studies comparing intravenous and topical Ketamine to placebo in CRPS patients reported baseline and post-treatment intensity of spontaneous pain [25, 26] and were included in the meta-analysis. There was no statistical heterogeneity (Q p= 0.354; I2 = 0%) and fixed effect model was used to report pooled results. Ketamine was statistically significant better than placebo in reducing pain intensity in CRPS patients (SDM = -1.012; 95% CI = -1.482 to -0.542; p <.001). An overall negative standardized difference in means (SDM) represents a favorable result with a larger decrease in pain intensity in the NMDA group compared to the placebo group (Figure 4).

3.5. NMDA Receptor Antagonist Effect in Pain

PHN: De Barros et al. [13] results showed an effect of time on pain intensity in PHN patients when comparing S-ketamine to placebo. The significant differences were seen with the Numerical Verbal Scale (NVS) recordings during the times between the medical appointments versus at the moment of the medical appointments. According to the authors, the significant correlation between the current NVS scores concerning medical appointment times was believed to relate to the Hawthorne effect (or observer effect) rather than the treatment studied. More specifically it is suspected that participants showed behavioral changes simply in response to the awareness of being observed. Pain scores themselves (measured via NVS), showed no statistical differences for S-Ketamine or placebo use.

The Eide et al. [14] study did conclude that unlike morphine or saline, low-dose IV Ketamine significantly reduced allodynia and wind-up-like pain in PHN patients utilizing a 100 mm VAS. On the other hand, PHN patients studied by Eisenberg et al. [15] showed no significant differences in pain reduction when receiving either oral Memantine or a placebo. The PHN patients in the Galer et al. [17] study received either 100mg/day of Riluzole, 200mg/day of Riluzole or placebo. Intervention with either oral Riluzole or placebo showed no significant changes in pain reduction. The neuropathic pain patients participating in the Jørum et al. [19] study received Ketamine and Alfentanil in a crossover fashion; authors concluded that both drugs reduced spontaneous and evoked pain, including the single PHN patient.

Facial neuropathy: Gilron et al. [18] found little or efficacy of high-dose Dextromethorphan in facial neuralgias. The authors' opinion was that the maximum therapeutic dose of Dextromethorphan provided only limited blockade of the NMDA receptor, thus limiting its efficacy in treating facial neuropathies.

CRPS: According to Finch et al. [16], topical Ketamine does not reduce pain in CRPS patients, but does show a reduction of allodynia. Positive results were seen in the Schwartzman et al. [25] study in which intravenous Ketamine (even at a low dosage), administered to CRPS patients in an outpatient setting resulted in statistically significant decreased pain. This pain reduction parameters were demonstrated with use of a short form McGill pain questionnaire and many were evaluated in the pain questionnaire that included most common sites of pain, burning pain, allodynia and overall pain. Data extracted from the activity watch confirmed decreased daytime pain scores. Spontaneous burning pain was also reduced in CRPS patients. Finally, Sigtermans et al. [26] found significant differences in pain reduction between Ketamine and placebo which were maintained until week 11, by week 12, Ketamine's treatment effect lost significance in CRPS patients [26].

Studies including a mix of conditions: Leung et al. [20] studied the treatment with both Alfentanil and Ketamine in neuropathic pain conditions that included PHN and found a reduction in stroking-evoked allodynic areas. Only the Ketamine infusion demonstrated a significant reduction in the von Frey evoked allodynic area [20]. According to Lynch et al. [21], no pain differences resulted in PHN, diabetic neuropathy and post-surgical neuropathic pain patients with the use of a topical cream containing placebo, 2% Amitriptyline, 1% Ketamine, or a combination of 2% Amitriptyline and 1% Ketamine. No pain relief was seen in any of the McQuay et al. [22] groups that included PHN and diabetic neuropathy patients receiving either oral Dextromethorphan or placebo. The Nelson et al. [23] study did not show pain reduction in the PHN group, but did show promise for the diabetic neuropathy group. Sang et al. [24] found there was no effect of age, pain duration, duration of diabetes, level of PHN, or characteristic of pain on treatment

effects. Jørum et al. [19] utilized Ketamine and Alfentanil in a crossover fashion and in this, authors concluded that both drugs reduced spontaneous and evoked pain, including the single PHN patient.

Other conditions: The Ayesh et al. [11] study showed no changes in pain over time or between intra-articular injections of Ketamine or normal saline on TMJ arthralgia patients. The atypical odontalgia patients studied by Baad-Hansen et al. [12], had no pain differences between treatments with S-Ketamine and fentanyl.

3.6. NMDA Receptor Antagonist Effect in other Outcomes

PHN: Eide et al. [14] found no significant changes in the thresholds for warm, cold, heat pain or tactile sensation with Ketamine or Morphine. However, Ketamine did normalize abnormal heat pain sensations in 4 patients, probably due to a central effect. Both wind-up pain and pain evoked by allodynia were significantly inhibited by Ketamine [14]. In the Eisenberg et al. [15] study, all forms of evoked pain tested were reduced but no significant differences between Memantine and placebo were detected. In addition, no statistically significant changes in thresholds were observed in either group [15]. All analyses of other secondary outcome measures showed no significant changes with the use of either Riluzole dosage or placebo according to Galer et al. [17]. Jørum et al. [19] found the cold pain detection threshold in the contralateral area not exhibiting symptoms to be notably reduced with use of intravenous Ketamine, when compared to the same site in age-matched normal controls. Heat pain detection thresholds were unchanged and without uniform heat hyperalgesia. Ketamine did not significantly reduce cold allodynia. Significant and marked reductions of hyperalgesia to cold were seen following Ketamine. It also significantly reduced ongoing pain and mechanical hyperalgesia. NMDA-receptor mediated central sensitization was found to be linked to cold hyperalgesia, but it is believed that there are other contributing mechanisms given that no changes were observed in the cold pain detection threshold [19].

Facial neuropathy: Although little to no pain efficacy was found by Gilron et al. [18] regarding the effects of Dextromethorphan on overall pain, a positive correlation was noticed between Dextromethorphan changes in pain-related interference with daily activities and changes in overall daily pain.

CRPS: While Finch et al. [16] found that topical Ketamine does not lead to pain reduction in patients with CRPS, results did show that topical Ketamine does cause a reduction in allodynia. The Schwartzman et al. [25] study showed a statistically significant reduction of pain in patients treated with Ketamine on: (1) the short form McGill pain questionnaire for the 3 month length of the study following treatment; (2) in several of the parameters evaluated in the pain questionnaire (pain in the most affected area, burning pain, pain when touched or brushed lightly and overall pain level; (3) data from the activity watch demonstrated fewer nighttime awakenings as well as lower daytime pain scores (only measured for 2 weeks following the last infusion); and (4) spontaneous burning pain decreased for 1 month. Changes in the other evaluated parameters included overall pain, deep muscle pain, joint pain, quantitative sensory testing and quality of life issues and none reached statistical significance. However, they did trend toward improvement in the Ketamine group [25]. The secondary outcomes measured in Sigtermans et al [26] showed significant improvement with Ketamine treatment compared to placebo treatment. These secondary outcome measures included: ability to use the affected limb in normal day-to-day activity for upper and lower limbs, active range of motion, threshold for touch on the affected and contralateral limbs, skin temperature of the affected and contralateral limbs, volumetric measurements of the affected and contralateral limbs [26].

Studies including a mix of conditions: Regarding Ketamine infusions, Leung et al. [20] noted dose-dependent increases in cold and cold pain thresholds and reductions in stroking pain scores. Ketamine infusions also showed a reduction in the stroking hyperalgesia area and a significant reduction in the von Frey hyperalgesia area. No significant central nervous system (CNS) side effects and changes in vital signs were noted [20]. Of the secondary endpoints evaluated by Sang et al. [24], statistically significant results were not yielded regarding the analysis of a six-category pain relief response or quality of life. There was no detectable effect in reduction of allodynia.

Other conditions: The Ayesh et al. [11] study reported decreased pressure pain threshold and decreased pressure pain tolerance after injections but without a difference between injections of Ketamine and normal saline. Baad-Hansen et al. [12], additionally found no difference between intravenous infusions of S-Ketamine, fentanyl and placebo regarding capsaicin-evoked pain.

4. Discussion

In this systematic review, Medline, The Cochrane Database and Web of Science databases were searched for randomized controlled trials comparing NMDA receptor antagonists to placebo intervention. Studies not written in English were excluded and the Embase database was not searched as the review authors did not have access at the time of this review. Stimulus induced evoked pain studies were not included in our review. It must be considered that evoked pain may respond to NMDA receptor antagonists differently than spontaneous neuropathic pain. Therefore, conclusions of our study may only apply to spontaneous neuropathic pain.

Table 3. Quality of the evidence and summary of findings (GRADE)

Oral Memantine compared to placebo for post-herpetic neuralgia				
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Anticipated absolute effects	
			Risk with Placebo	Risk difference with oral Memantine (95% CI)
Change in pain intensity VAS	54 (2 studies) 3-6 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	----	The mean change in pain intensity in the oral Memantine group was 0.092 standard deviations lower (0.627 lower to 0.442 higher)
Ketamine compared to placebo for the treatment of CRPS				
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Anticipated absolute effects	
			Risk with Placebo	Risk difference with Ketamine (95% CI)
Change in pain intensity VAS	79 (2 studies) 1-2 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	-----	The mean change in pain intensity in the intervention groups was 1.012 standard deviations lower (1.482 to 0.542 lower)
CI: Confidence interval;				
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.				
[1] Two studies at unclear or high risk of bias [2] Small number of studies (n=2) with small sample size				

Despite the small favorable effects seen in reducing pain by treating CRPS patients with ketamine, evidence in favor of NMDA receptor antagonists is lacking. Large high quality RCTs with a low risk of bias providing data on homogeneous interventions and outcomes are needed. The final quality of our data from meta-analyses is low. This is due to the fact there were only two studies in each meta-analysis (Table 3). Additionally, each meta-analysis included a study with unclear risk of bias and a study with high risk of bias and small sample size. Despite 16 studies meeting the inclusion criteria, only 4 could be used for meta-analyses. There was a lot of variation in interventions, route of administration and spontaneous neuropathic pain disorder studied. This limited the data set available for comparison. The available evidence to date does not support NMDA receptor antagonists as a first line treatment for spontaneous neuropathic pain disorders.

4.1. Agreements and Disagreements with Other Reviews

Only primary research RCTs were included in this systematic review with meta-analyses. In the process of inclusion/exclusion, seventy reviews were excluded from our original search strategy. Of these seventy reviews, two were duplicates and thirty-two were excluded since the authors studied a different condition than PHN, CRPS, facial neuropathy, atypical odontalgia and TMJ arthralgia (n=12), different intervention – not NMDA antagonists (n=17), not in English (n=1), a cost-benefit analysis (n=1), or an editorial or opinion letter (n=1). Thirty-six articles were examined for further review. Of those thirty-six included reviews, twelve were related to PHN, sixteen related to CRPS, three included information pertaining to other neuropathies including trigeminal neuralgia and five were combinations of two or more different neuropathies (PHN and CRPS or PHN and other neuropathies).

According to the American Chronic Pain Association Consumer Guide to Pain Medication and Treatment, ketamine is the strongest of the NMDA receptor antagonists [27]. According to Niesters and Dahan [28], systematic reviews and meta-analyses support the efficacy of ketamine treatment of CRPS. Eide et al. [14] concluded that ketamine reduces pain in patients with PHN as well as inhibits allodynia and wind-up like pain. The authors further stated that ketamine appears to exhibit its effects on the quality of the tactile and warm sensations during sensory testing, but does not seem to affect sensory thresholds.

Dextromethorphan, Memantine, Riluzole, Amantadine, GV196771 and MK-801 have a weaker affinity for the receptor, slightly different binding sites, minimizing their side effect profile in treating PHN and CRPS [29–31]. These weaker NMDA receptor antagonists were deemed ineffective in prior reviews in treating PHN [17, 18, 23, 31, 32]. High dose IV ketamine is most effective but its side

effects limits its uses and confines it often to in-patient procedures [33]. In patients who respond to a NMDA receptor antagonist for their pain of neuropathic origin, the high doses needed are limited by its toxicity [33].

All included reviews [29, 31, 33–66] agreed that more research of higher quality is necessary to truly assess the effectiveness of this class of drugs against specific neuropathic conditions. There are positive findings for the use of ketamine in treating opioid-resistant CRPS [67]. But due to a lack of convincing evidence routine administration of NMDA receptor antagonists as a first- or even second-line treatment of neuropathic pain cannot be supported now. Hocking and Cousins [33] concluded that NMDA receptor antagonists are best reserved as a third-line treatment in patients who do not respond to standard pharmacotherapy.

4.2. Conclusions

Since the studies evaluated multiple pain conditions and the same NMDA receptor antagonist was not used in each study, nor were the receptor antagonists administered in the same manner, comparing and summarizing data was difficult. This narrowed the meta analyses to only four of the sixteen studies [15, 24–26]. The lack of homogenous data and small sample sizes constrained the ability to draw conclusions about the efficacy of NMDA receptor antagonists in treating spontaneous neuropathic pain in the orofacial region. Additional research in this area is needed, with higher quality of studies and less heterogeneity of the patient populations.

Acknowledgements

Drs. B.J. Larsen and K.J. Mau contributed equally to this study as first co-authors. Authors acknowledge Drs. Margarita Zeichner-David and Dr. Gayle Macdonald for help with editing and formatting of the manuscript.

REFERENCES

[1] M. Costigan, J. Scholz, and C. J. Woolf, "Neuropathic pain: a maladaptive response of the nervous system to damage," *Annu. Rev. Neurosci.*, vol. 32, pp. 1–32, 2009.

[2] J. N. Campbell and R. A. Meyer, "Mechanisms of neuropathic pain," *Neuron*, vol. 52, no. 1, pp. 77–92, Oct. 2006.

[3] F. T. Nickel, F. Seifert, S. Lanz, and C. Maihöfner, "Mechanisms of neuropathic pain," *Eur. Neuropsychopharmacol*, vol. 22, no. 2, pp. 81–91, 2012

[4] G. J. Bennett, "Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor," *J. Pain Symptom Manage.*, vol. 19, no. 1 Suppl, pp. S2-6, Jan. 2000.

[5] H. Smits, M. Van Kleef, J. Holsheimer, and E. A. J. Joosten, "Experimental Spinal Cord Stimulation and Neuropathic Pain: Mechanism of Action, Technical Aspects, and Effectiveness," vol. 13, no. 2, pp. 154–168, 2013.

[6] S. Collins, M. J. Sigtermans, A. Dahan, W. W. A. Zuurmond, and R. S. G. M. Perez, "NMDA Receptor Antagonists for the Treatment of Neuropathic Pain," *Pain Med.*, vol. 11, no. 11, pp. 1726–1742, Nov. 2010.

[7] S. H. Sindrup and T. S. Jensen, "Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action," *Pain*, vol. 83, no. 3, pp. 389–400, Dec. 1999.

[8] F. Coluzzi and C. Mattia, "Mechanism-based treatment in chronic neuropathic pain: The role of antidepressants," *Curr. Pharm. Des.*, vol. 11, no. 23, pp. 2945–2960, 2005.

[9] A. Liberati, D. G. Altman, J. Tetzlaff, C. Mulrow, P. C. Gøtzsche, and P. A. John, "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration," *BMJ*, pp. 339, Jul. 2009.

[10] J. Higgins and S. (editors) Green, "Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]," 2011.

[11] E. E. Ayesh, T. S. Jensen, and P. Svensson, "Effects of intra-articular Ketamine on pain and somatosensory function in temporomandibular joint arthralgia patients," *Pain*, vol. 137, no. 2, pp. 286–94, Jul. 2008.

[12] L. Baad-Hansen, G. I. Juhl, T. S. Jensen, B. Brandsborg, and P. Svensson, "Differential effect of intravenous S-Ketamine and fentanyl on atypical odontalgia and capsaicin-evoked pain," *Pain*, vol. 129, no. 1–2, pp. 46–54, May 2007.

[13] G. A. M. de Barros, H. A. H. A. Miot, A. M. Braz, F. F. Ramos, and M. A. Borges, "Topical (S)-Ketamine for pain management of postherpetic neuralgia," *An. Bras. Dermatol.*, vol. 87, no. 3, pp. 504–505, Jan. 2012.

[14] P. K. Eide, E. Jorum, A. Stubhaug, J. Bremnes, and H. Breivik, "Relief Of Postherpetic Neuralgia With The N-Methyl-D-Aspartic Acid Receptor Antagonist Ketamine - A Double-Blind, Cross-Over Comparison With Morphine And Placebo," *Pain*, vol. 58, no. 3, pp. 347–354, Sep. 1994.

[15] E. Eisenberg, A. Kleiser, A. Dortort, T. Haim, and D. Yarnitsky, "The NMDA (N-methyl-D-aspartate) receptor antagonist Memantine in the treatment of postherpetic neuralgia: a double-blind, placebo-controlled study," *Eur. J. Pain-London*, vol. 2, no. 4, pp. 321–327, 1998.

[16] P. M. Finch, L. Knudsen, and P. D. Drummond, "Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical Ketamine," *Pain*, vol. 146, no. 1–2, pp. 18–25, Nov. 2009.

[17] B. S. Galer, L. L. Twilling, J. Harle, R. S. Cluff, E. Friedman, and M. C. Rowbotham, "Lack of efficacy of riluzole in the treatment of peripheral neuropathic pain conditions," *Neurology*, vol. 55, no. 7, pp. 971–975, Oct. 2000.

[18] I. Gilron, S. L. Booher, M. S. Rowan, M. S. Smoller, and M. B. Max, "A randomized, controlled trial of high-dose Dextromethorphan in facial neuralgias," *Neurology*, vol. 55, no. 7, pp. 964–71, Oct. 2000.

[19] E. Jørum, T. Warncke, and A. Stubhaug, "Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist Ketamine--a double-blind, cross-over comparison with Alfentanil and placebo," *Pain*, vol. 101, no. 3, pp. 229–35, Feb. 2003.

[20] A. Leung, M. S. Wallace, B. Ridgeway, and T. Yaksh, "Concentration-effect relationship of intravenous Alfentanil and Ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain," *Pain*, vol. 91, no. 1–2, pp. 177–187, Mar. 2001.

[21] M. E. Lynch, A. J. Clark, J. Sawynok, and M. J. L. Sullivan, "Topical 2% amitriptyline and 1% Ketamine in neuropathic pain syndromes - A randomized, double-blind, placebo-controlled trial," *Anesthesiology*, vol. 103, no. 1, pp. 140–146, Jul. 2005.

[22] H. J. McQuay, D. Carroll, R. Jadad, C. J. Glynn, T. Jack, R. a Moore, and P. J. Wiffeh, "Dextromethorphan for the treatment of neuropathic pain: A double-blind randomised controlled crossover trial with integral n-of-1 design," *Pain*, vol. 59, no. 1, pp. 127–33, 1994.

[23] K. A. Nelson, K. M. Park, E. Robinovitz, C. Tsigos, and M. B. Max, "High-dose oral Dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia," *Neurology*, vol. 48, no. 5, pp. 1212–1218, May 1997.

[24] C. N. Sang, S. Booher, I. Gilron, S. Parada, and M. B. Max, "Dextromethorphan and Memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials," *Anesthesiology*, vol. 96, no. 5, pp. 1053–61, May 2002.

[25] R. J. Schwartzman, G. M. Alexander, J. R. Grothusen, T. Paylor, E. Reichenberger, and M. Perreault, "Outpatient intravenous Ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study," *Pain*, vol. 147, no. 1–3, pp. 107–115, Dec. 2009.

[26] M. J. Sigtermans, J. J. van Hilten, M. C. R. Bauer, M. S. Arbous, J. Marinus, E. Y. Sarton, and A. Dahan, "Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1," *Pain*, vol. 145, no. 3, pp. 304–311, Oct. 2009.

[27] S. Feinberg, J. Christian, B. Darnall, R. Feinberg, D. Kalauokalani, and C. Pasero, "ACPA Resource Guide to Chronic Pain Medication & Treatment," Am. Chronic Pain Assoc., p. 135, 2015.

[28] M. Niesters and A. Dahan, "Pharmacokinetic and pharmacodynamic considerations for NMDA receptor antagonists in the treatment of chronic neuropathic pain," *Expert Opinion on Drug Metab. & Toxic.,* vol. 8, no. 11, 2012.

[29] R. N. Harden, A. L. Oaklander, A. W. Burton, R. S. G. M. Perez, K. Richardson, M. Swan, J. Barthel, B. Costa, J. R. Graciosa, and S. Bruehl, "Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition," *Pain Med.,* vol. 14, no. 2, pp. 180–229, Feb. 2013.

[30] K. Hempenstall, T. J. Nurmikko, R. W. Johnson, R. P. A'Hern, and A. S. C. Rice, "Analgesic therapy in postherpetic neuralgia: a quantitative systematic review," *PLoS Med.*, vol. 2, no. 7, p. e164, Jul. 2005.

[31] N. Attal, "Pharmacologic treatment of neuropathic pain," *Acta Neurol. Belg.,* vol. 101, no. 1, pp. 53–64, Mar. 2001.

[32] L. Nikolajsen, H. Gottrup, A. G. D. Kristensen, and T. S. Jensen, "Memantine (a N-methyl-D-aspartate receptor antagonist) in the treatment of neuropathic pain after amputation or surgery: A randomized, double-blinded, cross-over study," *Anesth. Analg.,* vol. 91, no. 4, pp. 960–966, Oct. 2000.

[33] G. Hocking and M. J. Cousins, "Ketamine in chronic pain management: an evidence-based review," *Anesth. Analg.,* vol. 97, no. 6, pp. 1730–9, Dec. 2003.

[34] C. E. Argoff, N. Katz, and M. Backonja, "Treatment of postherpetic neuralgia: a review of therapeutic options," *J. Pain Symptom Manage.*, vol. 28, no. 4, pp. 396–411, Oct. 2004.

[35] N. Attal, G. Cruccu, M. Haanpää, P. Hansson, T. S. Jensen, T. Nurmikko, C. Sampaio, S. Sindrup, and P. Wiffen, "EFNS guidelines on pharmacological treatment of neuropathic pain," *Eur. J. Neurol.,* vol. 13, no. 11, pp. 1153–69, Nov. 2006.

[36] P. Azari, D. R. Lindsay, D. Briones, C. Clarke, T. Buchheit, and S. Pyati, "Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review," *CNS Drugs*, vol. 26, no. 3, pp. 215–28, Mar. 2012.

[37] M. M. Backonja and J. Serra, "Pharmacologic management part 1: Better-studied neuropathic pain diseases," *Pain Med.,* vol. 5, no. 1, pp. S28–S47, Mar. 2004.

[38] A. Ben-Ari, M. C. Lewis, and E. Davidson, "Chronic administration of ketamine for analgesia." *J. Pain Palliat. Care Pharmacother*., vol. 21, no. 1, pp. 7–14, Jan. 2007.

[39] J.-M. Berthelot, "Current management of reflex sympathetic dystrophy syndrome (complex regional pain syndrome type I)," *Joint Bone Spine*, vol. 73, no. 5, pp. 495–499, Oct. 2006.

[40] F. Birklein, D. O'Neill, and T. Schlereth, "Complex regional pain syndrome: An optimistic perspective," *Neurology*, vol. 84, no. 1, pp. 89–96, Jan. 2015.

[41] C. Bonezzi and L. Demartini, "Treatment options in postherpetic neuralgia," *Acta Neurol. Scand. Suppl.,* vol. 173, pp. 25-35-52, Jan. 1999.

[42] S. Bruehl, "Complex regional pain syndrome," *BMJ-British Med. J.,* vol. 351, Jul. 2015.

[43] M. S. Chong and B. Brandner, "Neuropathic agents and pain. New strategies," *Biomed. Pharmacother.,* vol. 60, no. 7, pp. 318–322, Aug. 2006.

[44] P. J. Christo, G. Hobelmann, and D. N. Maine, "Post-herpetic neuralgia in older adults: evidence-based approaches to clinical management," *Drugs Aging*, vol. 24, no. 1, pp. 1–19, Jan. 2007.

[45] S. Collins, M. J. Sigtermans, A. Dahan, W. W. A. Zuurmond, and R. S. G. M. Perez, "NMDA receptor antagonists for the treatment of neuropathic pain," *Pain Med.,* vol. 11, no. 11, pp. 1726–42, Nov. 2010.

[46] S. B. Connolly, J. P. Prager, and R. N. Harden, "A Systematic Review of Ketamine for Complex Regional Pain Syndrome," *Pain Med.*, vol. 16, no. 5, pp. 943–969, May 2015.

[47] G. Cruccu, "Treatment of painful neuropathy," *Curr. Opin. Neurol.,* vol. 20, no. 5, pp. 531–5, Oct. 2007.

[48] A. Dahan, E. Olofsen, and M. Niesters, "Pharmacotherapy for pain: efficacy and safety issues examined by subgroup analyses," *Pain*, vol. 156 Suppl, pp. S119-26, Apr. 2015.

[49] M. W. Douglas, R. W. Johnson, and A. L. Cunningham, "Tolerability of treatments for postherpetic neuralgia," *Drug Saf.,* vol. 27, no. 15, pp. 1217–33, Jan. 2004.

[50] R. M. Dubinsky, H. Kabbani, Z. El-Chami, C. Boutwell, and H. Ali, "Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology," *Neurology*, vol. 63, no. 6, pp. 959–65, Sep. 2004.

[51] N. B. Finnerup, M. Otto, H. J. McQuay, T. S. Jensen, and S. H. Sindrup, "Algorithm for neuropathic pain treatment: An evidence based proposal," *Pain,* vol. 118, no. 3, pp. 289–305, Dec. 2005.

[52] N. B. Finnerup and T. S. Jensen, "Mechanisms of Disease: mechanism-based classification of neuropathic pain - a critical analysis," *Nat. Clin. Pract. Neurol.,* vol. 2, no. 2, pp. 107–115, Feb. 2006.

[53] M. Freedman, A. C. Greis, L. Marino, A. N. Sinha, and J. Henstenburg, "Complex Regional Pain Syndrome Diagnosis and Treatment," *Phys. Med. Rehabil. Clin. N. Am.,* vol. 25, no. 2, pp. 291+, May 2014.

[54] R. N. Harden, "Pharmacotherapy of complex regional pain syndrome," *Am. J. Phys. Med. Rehabil.,* vol. 84, no. 3, S, pp. S17–S28, Mar. 2005.

[55] K. Hempenstall, T. J. Nurmikko, R. W. Johnson, R. P. A'Hern, and A. S. C. Rice, "Analgesic therapy in postherpetic neuralgia: A quantitative systematic review," *PLOS Med.,* vol. 2, no. 7, pp. 628–644, Jul. 2005.

[56] R. W. Johnson and T. L. Whitton, "Management of herpes zoster (shingles) and postherpetic neuralgia," *Expert Opin. Pharmacother.,* vol. 5, no. 3, pp. 551–559, Mar. 2004.

[57] W. S. Kingery, "A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes," *Pain*, vol. 73, no. 2, pp. 123–39, Nov. 1997.

[58] M. T. Mendlik and T. J. Uritsky, "Treatment of Neuropathic Pain," *Curr. Treat. Options Neurol.,* vol. 17, no. 12, pp. 50, Dec. 2015.

[59] E. O. Neil, M. W. Benedict, J. McAuley, L. Marston, and G. L. Moseley, "Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews," *Cochrane Database Syst Rev*. 2013 Apr 30;(4):CD009416.

[60] Z. Paster and C. M. Morris, "Treatment of the localized pain of postherpetic neuralgia," *Postgrad. Med.,* vol. 122, no. 1, pp. 91–107, Jan. 2010.

[61] D. R. Robertson and C. F. George, "Treatment of post herpetic neuralgia in the elderly," *Br. Med. Bull.,* vol. 46, no. 1, pp. 113–23, Jan. 1990.

[62] J. Sawynok, "Topical Analgesics for Neuropathic Pain in the Elderly: Current and Future Prospects," *Drugs Aging*, vol. 31, no. 12, pp. 853–862, Dec. 2014.

[63] J. Sawynok, "Topical and peripheral ketamine as an analgesic," *Anesth. Analg.,* vol. 119, no. 1, pp. 170–8, Jul. 2014.

[64] E. Soto, D. R. Stewart, A. J. Mannes, S. L. Ruppert, K. Baker, D. Zlott, D. Handel, and A. M. Berger, "Oral ketamine in the palliative care setting: a review of the literature and case report of a patient with neurofibromatosis type 1 and glomus tumor-associated complex regional pain syndrome," *Am. J. Hosp. Palliat. Care*, vol. 29, no. 4, pp. 308–17, Jun. 2012.

[65] M. M. Wertli, A. G. H. Kessels, R. S. G. M. Perez, L. M. Bachmann, and F. Brunner, "Rational pain management in complex regional pain syndrome 1 (CRPS 1)--a network meta-analysis," *Pain Med.,* vol. 15, no. 9, pp. 1575–89, Sep. 2014.

[66] A. Żyluk and J. Pastuszka, "Intravenous ketamine infusions for chronic algodystrophy: a review," *Polish Orthop. Traumatol.,* vol. 79, pp. 37–40, Jan. 2014.

[67] J.-M. Berthelot, "Current management of reflex sympathetic dystrophy syndrome (complex regional pain syndrome type I)," *Joint. Bone. Spine*, vol. 73, no. 5, pp. 495–9, Oct. 2006.