REVIEW ARTICLE

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Efficacy and Safety of Ketamine in Patients with Complex Regional Pain Syndrome

A Systematic Review

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Abstract

Despite being a recognized clinical entity for over 140 years, complex regional pain syndrome (CRPS) remains a difficult-to-treat condition. While there have been multiple therapies explored in the treatment of CRPS, NMDA antagonists such as ketamine continue to hold significant interest because of their potential ability to alter the central sensitization noted in chronic pain states. The objective of this review is to identify published literature for evidence of the efficacy and safety of ketamine in the treatment of CRPS.

PubMed and the Cochrane Controlled Trials Register were searched (final search 26 May 2011) using the MeSH terms 'ketamine', 'complex regional pain syndrome', 'analgesia' and 'pain' in the English literature. The manuscript bibliographies were then reviewed to identify additional relevant papers. Observational trials were evaluated using the Agency for Healthcare Research and Quality criteria; randomized trials were evaluated using the methodological assessment of randomized clinical trials.

The search methodology yielded three randomized, placebo-controlled trials, seven observational studies and nine case studies/reports. In aggregate, the data available reveal ketamine as a promising treatment for CRPS. The

optimum dose, route and timing of administration remain to be determined. Randomized controlled trials are needed to establish the efficacy and safety of ketamine and to determine its long-term benefit in CRPS.

1. Introduction

Complex regional pain syndrome (CRPS) has had many names throughout the years, reflecting contemporary understanding of the condition.[1,2] It was first described over 100 years ago as 'causalgia' and subsequently has carried multiple other descriptors such as 'reflex sympathetic dystrophy', 'Sudeck's atrophy', 'algodystrophy' and 'neurodystrophy'. Finally, the term 'complex regional pain syndrome' was adopted in 1994 by the International Association for the Study of Pain (IASP), conceding that the pathophysiology and diagnosis were in fact much more complicated than previously acknowledged.[3,4]

CRPS is a condition that can occur after a noxious event, or brain or spinal cord injury and it has a reported incidence rate of from 5.46 to 26.2 per 100 000 persons.[2,5,6] The basic features of CRPS include pain disproportionate to the injury, allodynia and hyperalgesia, and autonomic abnormalities.[4,7] The IASP published descriptive criteria for CRPS in 1994 (table I). The low specificity of the IASP criteria led to the development and validation of the Budapest criteria (table II), which is the currently accepted and international standard for the diagnosis of CRPS.[9,10]

The pathophysiology of CRPS is still not fully understood, and it involves the complex interaction of many factors. One of the hallmarks of CRPS is that of central sensitization. This is caused by a reduction in the firing threshold of Aδ and C fibres leading to the ongoing release of neurotransmitters and peptide neuromodulators from peripheral afferent terminals.[11,12] As a result of an inciting injury, Aδ and C fibres become surrounded by a complex microenvironment of neurotrophic factors, cytokines, prostaglandins, proteins, bradykinins, nitric oxide, nitric oxide synthase, calcitonin gene-related peptide, endothelin-1, tumour necrosis factor (TNF)-α, interleukins, substance P and endothelium-dependent vasodilator neuropeptides, which then collectively activate intracellular phosphokinase A and C.[13-27] Phosphokinase A and C in turn phosphorylate tetrodotoxin-resistant sensory neuron-specific sodium channels, which causes peripheral sensitization of nociceptive afferents.[28]

This constant level of depolarization accumulates through multiple activated signalling cascades and leads to the blockade of magnesium ions on the NMDA receptors. The suppression of magnesium ions activates the NMDA receptors, causing the release of calcium through the activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and the kainate ligand-gated ion channels.[29,30] This in turn increases the depolarization of the pain pathways and amplification of the pain signal, leading to central sensitization.[29] Thus, a low level of pain signal transmission remains constant even if the inciting noxious stimulation is removed.

The NMDA receptor antagonists, such as ketamine, are an attractive option in the treatment of CRPS because they can possibly reverse central sensitization and alter neural plasticity.[31] There is now a growing body of evidence in the literature suggesting that ketamine can in fact help in the treatment of neuropathic conditions and even postoperative pain.[32-34] This article, unlike previous reviews, will examine the entire body of literature available to determine the

Table I. International Association for the Study of Pain (IASP) diagnostic criteria for complex regional pain syndrome (CRPS) [these criteria have been reproduced from Merskey and Bogduk,[8] with permission of the IASP; the criteria may not be reproduced for any other purpose without permission]

1. A preceding noxious event without obvious nerve lesion (CRPS I) or with obvious nerve lesion (CRPS II)
2. Continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event
3. Evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of pain
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Table II. Budapest clinical diagnostic criteria for complex regional pain syndrome (reproduced from Harden et al.,[9] with permission)

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories:
sensory: reports of hyperaesthesia and/or allodynia
vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry
motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories:
sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry
sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry
motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
4. There is no other diagnosis that better explains the signs and symptoms

efficacy and safety of ketamine in the treatment of CRPS.[35]

2. Literature Search Methodology

2.1 Systematic Literature Search

PubMed and the Cochrane Controlled Trials Register were searched using the MeSH terms 'ketamine', 'complex regional pain syndrome', 'analgesia' and 'pain' in the English literature. The search was limited to human trials and included all trials indexed before 26 May 2011. Data from animal studies, abstracts and letters were excluded. The manuscript bibliographies were then reviewed to identify additional relevant papers. We evaluated all case reports, as well as retrospective, prospective and randomized controlled trials. Each randomized and observational study received a score based on their design, intervention performed, follow-up and data extraction. Randomized trials were evaluated using generally accepted principles of intervention research as shown in the methodological assessment of randomized clinical trials by Koes et al.[36] (table III), whereas observational studies were evaluated using the Agency for Healthcare Research and Quality (AHRQ) criteria[40] (table IV). It was determined that studies with scores >50 (based on either scoring criteria) would be included in our evaluation.

2.2 Qualitative Analysis

Table V illustrates the five levels of qualitative analysis used to measure the effectiveness of ketamine in treating CRPS. For the randomized, placebo-controlled studies, a positive outcome was defined as ketamine being more efficacious than the control in providing pain relief. In the observational studies, a positive outcome was defined as pain relief with the use of ketamine.

2.3 Recommendations

Grading recommendations were based on criteria by Guyatt et al.,[49] as listed in table VI.

3. Evidence for the Use of Ketamine in Complex Regional Pain Syndrome

The systematic literature search yielded three randomized, placebo-controlled trials, seven observational studies and nine case reports/series evaluating the efficacy of ketamine in the treatment of CRPS (tables VII and VIII). These studies show that ketamine has both acute efficacy and long-term implications in the management of complex regional pain. Details from relevant studies are summarized in the following sections.

3.1 Efficacy

The three randomized trials included in this review were performed by Finch et al.,[34] Schwartzman

et al.[39] and Sigtermans et al.[38] In the study by Schwartzman et al.,[39] it was shown that the CRPS patients treated with intravenous ketamine had a 27% decrease in their scores on the numerical rating scale for pain, compared with 2% in the placebo group. In this study there was also a statistically significant reduction of pain in the ketamine group, as measured by the Short-Form McGill Pain Questionnaire, decreased night-time awakening and decreased spontaneous burning pain in the treatment group.[39] After a mean 4.2-day course of continuous intravenous ketamine infusion, Sigtermans et al.[38] showed that scores on the numerical rating scale for pain were significantly lower in the treatment group than in the placebo group periodically over a 12-week period. This study concluded that the lowest pain scores were 1 week after the ketamine treatment.

In another randomized, crossover, placebo-controlled study by Finch et al.,[34] topical 10% ketamine was used in patients with CRPS twice in a period separated by 1 week and compared with placebo. This study concluded that topical ketamine did not lead to pain reduction in patients

Table III. Methodological assessment of randomized clinical trials, using criteria adapted from Koes et al.[37]

Criteria		Weighted score (points)	Scores for identified studies		
			Sigtermans et al.[38]	Schwartzman et al.[39]	Finch et al.[34]
A	Homogeneity: description of inclusion and exclusion criteria (1 point); restriction to an homogeneous population (1 point)	2	2	2	2
B	Comparability of relevant baseline characteristics: duration of complaints, value of outcome measures, age, recurrence status and radiating complaints (1 point each)	5	5	5	5
C	Randomization procedure: randomization procedure described (2 points); randomization procedure excludes bias (2 points)	4	4	4	2
D	Drop-outs: described for each study group separately (3 points)	3	3	3	3
E	<20% loss for follow-up (2 points)	2	2	2	2
	<10% loss for follow-up (2 points)	2	2	2	2
F	>50 subjects in the smallest group (8 points)	8	0	0	0
	>100 subjects in the smallest group (9 points)	9	0	0	0
G	Interventions: included in protocol and described (5 points); all reference treatments explicitly described (5 points)	10	10	10	10
H	Pragmatic study: comparison with an existing treatment modality (5 points)	5	0	0	0
I	Co-interventions: avoided or similar; other medical interventions are avoided in the design of the study (except analgesics, advice on posture or use at home of heat, rest or routine exercise scheme) [5 points]	5	5	5	5
J	Placebo-controlled: attempt at blinding (3 points); successful blinding (2 points)	5	5	5	5
K	Attempt to blind patients (3 points); successful blinding (2 points)	5	5	5	5
L	Outcome measures: relevant and included measurements of pain, improvement in global measure, functional status, activity and adverse effects (2 points each)	10	8	8	8
M	Blinded outcome assessments (effect measurement by a blinded assessor)	10	10	10	10
N	Follow-up period adequate: moment of measurement during or just after treatment (3 points); moment of measurement 6 mo or longer (2 points)	5	3	3	3
O	Intent-to-treat analysis: when loss to follow-up is <10%, relating to all randomized patients for most important outcome measures and on moments of effect measurement minus missing values (excluding non-compliance and co-interventions) [5 points]	5	5	5	5
P	Frequencies of most important outcomes presented for each treatment group with mean or median with standard error or percentiles (5 points)	5	5	5	5
Total score		**100**	**74**	**74**	**72**

Table IV. Assessment of observational studies, using modified Agency for Healthcare Research and Quality criteria[36]

Criteria		Weighted score (points)	Scores for identified studies						
			Kiefer et al.[41]	Sigtermans et al.[42]	Goldberg et al.[43]	Correll et al.[44]	Kiefer et al.[45]	Goldberg et al.[46]	Koffler et al.[47]
1	**Study question**	**2**							
	Clearly focused and appropriate	2	2	2	2	2	2	2	2
2	**Study population**	**8**							
	Description	5	5	5	5	5	5	5	5
	Sample size justification	3	0	0	0	0	0	0	1
3	**Comparability of subjects**	**22**							
	Specific inclusion/exclusion criteria for all groups	5	5	5	2	1	5	5	5
	Criteria applied equally to all groups	3	3	3	3	3	3	3	3
	Comparability of groups at baseline with regard to disease status and prognostic factors	3	3	3	3	1	3	3	3
	Study groups comparable to non-participants with regard to confounding factors	3	0	0	0	0	0	0	0
	Use of concurrent controls	5	0	2	0	0	0	0	0
	Comparability of follow-up among groups at each assessment (3 points); comparability of over half of the assessments (2 points); comparability of under half of the assessments (1 point)	3	3	3	3	2	3	3	3
4	**Exposure or intervention**	**11**							
	Clear definition	5	5	5	5	5	5	5	5
	Measurement method standard, valid and reliable	3	3	3	3	3	3	3	3
	Exposure measured equally in all study groups	3	3	3	3	3	3	3	3
5	**Outcome measures**	**20**							
	Primary/secondary outcomes clearly defined (5 points for clearly defined; 3 points for only primary outcome)	5	5	5	3	3	5	3	5
	Outcomes assessed blind to exposure or intervention	5	0	0	0	0	0	0	0
	Method of outcome assessment standard, valid and reliable (5 points); method outcome not reliable (0 points)	5	5	5	5	5	5	5	5
	Length of follow-up adequate for question (5 points for ≥6 mo; 3 points for 3 mo; 2 points for 1–3 mo; 1 point for <1 mo)	5	1	1	1	5	5	1	2
6	**Statistical analysis**	**19**							
	Statistical tests appropriate	5	5	5	5	5	5	5	5
	Multiple comparisons taken into consideration: 4 (4 points), 3 (3 points), 2 (2 points), 1 (1 point)	3	3	1	0	1	3	2	1
	Modelling and multivariate techniques appropriate	2	0	0	0	0	0	0	0
	Power calculation provided	2	0	0	0	0	0	0	0

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Table IV. Contd

	Criteria	Weighted score (points)	Scores for identified studies							
			Kiefer et al.[41]	Sigtermans et al.[42]	Goldberg et al.[43]	Correll et al.[44]	Kiefer et al.[45]	Goldberg et al.[46]	Koffler et al.[47]
	Assessment of confounding (5 points); mentioned confounding variables (1 point)	5	1	1	1	1	1	1	0
	Dose-response assessment, if appropriate	2	0	2	0	2	2	2	0
7	**Results**	8							
	Measure of effect for outcomes and appropriate measure of precision	5	5	5	5	3	2	3	3
	Adequacy of follow-up for each study group (3 points for all follow-up; 2 points for >50% follow-up; 1 point for <50% follow-up)	3	3	3	3	2	3	3	3
8	**Discussion**	5							
	Conclusions supported by results with possible biases and limitations taken into consideration (5 points); conclusion supported by results without consideration of biases and limitations (3 points)	5	3	3	3	5	5	5	5
9	**Funding or sponsorship**	5							
	Type and sources of support for study	5	0	0	0	0	0	0	0
10	**Total score**	100	63	64	55	57	68	62	62

with CRPS but it did reduce allodynia, which is an important aspect of this condition.

Among the seven observational studies, two were performed by Kiefer et al.[41,45] Interestingly, the first of these was a pilot study of four patients that failed to demonstrate the effectiveness of ketamine infusions in CRPS.[41] However, in the follow-up, open-label, phase II study, 20 patients received 5-day infusions of an anaesthetic dose of ketamine in combination with midazolam. It was concluded that ketamine demonstrated a significant benefit in reducing pain and associated movement disorders, and in improving quality of life and ability to work at 3–6 months.[45]

In the study by Koffler et al.,[47] at 6 weeks there was a marked reduction in pain in the ketamine-treated group and there were no adverse neurocognitive effects. In the prospective study performed by Goldberg et al.,[43] there was a significant reduction in pain following the 4-hour outpatient ketamine infusions, which were performed consecutively for 10 days. Another prospective study performed by Goldberg et al.[46] showed the effectiveness of a 5-day infusion, and one by Sigtermans et al.[42] showed the effectiveness of a 5-hour infusion of intravenous ketamine, in the treatment of CRPS. In the retrospective study by Correll et al.,[44] patients receiving a second treatment of intravenous ketamine infusion (with doses ranging from 10 to 50 mg/hour for a mean of 4.7 days) were shown to have longer periods of pain relief than patients treated with a single infusion. After a single ketamine infusion, 54% of 33 patients were pain free at 3 months and 31% remained pain free at 6 months. Following a repeat ketamine infusion, 58% of 12 patients had pain relief at 1 year and 33% remained pain free for more than 3 years.

3.2 Route of Administration

Of the studies reviewed, ketamine was most commonly administered intravenously. However, Finch et al.[34] and Ushida et al.[57] showed that topical administration of ketamine could be effective in the treatment of CRPS. Also, in the case study performed by Villanueva-Perez et al.,[50] oral ketamine was effective in the treatment of CRPS.

Table V. Quality of evidence developed by the US Preventive Services Task Force (USPSTF) [reproduced from Berg and Allan,[48] with permission]

I	Conclusive: evidence obtained from at least one properly randomized controlled trial
II–1	Strong: evidence obtained from well designed controlled trials without randomization
II–2	Moderate: evidence obtained from well designed cohort or case-control analytical studies, preferably from more than one centre or research group
II–3	Limited: evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
III	Intermediate: opinions of respected authorities, based on clinical experience, descriptive studies and case reports or reports of expert committees

3.3 Dose and Duration

There has been no consensus in the literature with reference to the dose and the duration needed for systemic administration or topical application of ketamine for the treatment of CRPS.[43,46] Reported durations of intravenous ketamine infusion have varied from hours to 10 days.[39,42,43,45-47] Ketamine doses have also varied greatly among the different studies. Intravenous infusion dosages have ranged from 0.35 μg/kg/hour to a high of 7 mg/kg/hour.[39,42-45,47] The titration of ketamine has also differed among the different studies; one study titrated in set intervals while others titrated to analgesia or feelings of inebriation.[39,42,44,45,47]

3.4 Adverse Effects

The adverse effects reported with ketamine include feelings of inebriation, nausea, psycho-

Table VI. Grading recommendations (reproduced from Guyatt et al.,[49] with permission)

Grade of recommendation/description		Benefit vs risk and burden	Methodological quality of supporting evidence	Implications
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risk and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or on patient or societal values
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risk and burdens	RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or on patient or societal values
2C	Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risk and burden; benefits, risk and burden may be closely balanced	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

RCT = randomized controlled trial.

Table VII. Qualitative evaluation of the studies included that assessed the efficacy of ketamine for the treatment of complex regional pain syndrome (CRPS)

Study	Study type	Patient selection	No. of patients	Intervention	Assessment tools	Assessment intervals	Results	Adverse effects	Conclusions
Schwartzman et al.[39]	Randomized, double-blind, placebo-controlled	CRPS diagnosis based on revised IASP criteria	19 (18 F); placebo (n=10); ketamine (n=9)	IV ketamine or NS for 4 h daily for 10 d, max dose of ketamine 0.35 mg/kg/h, both groups received midazolam and clonidine	NRS, MPQ, activity watch, thermal detection thresholds, thermal pain and cutaneous temperature, dynamic and static mechano-allodynia, deep pressure, motor function, QLQ	2 wk prior to and 1 and 3 mo post-treatment	Reduction in pain (27% in ketamine group; 2% in placebo)	Nausea, headache, dysphoria in 6/19 patients	Statistically significant reduction in pain in IV ketamine group. Not all patients had same degree of improvement in pain. Higher doses provided much longer analgesia
Sigtermans et al.[38]	Randomized, double-blind, parallel-group, placebo-controlled	CRPS I diagnosis based on IASP criteria	60 (48 F); placebo (n=30); ketamine (n=30)	IV ketamine (5–30 mg/h) or NS for 5 d	NRS, RASQ, WAQ, range of motion, threshold for touch, skin temperature, volumetric measurements	1, 3 and 12 wk	Better analgesia in ketamine group	Nausea, vomiting, psychotomimetic effects	Reduction in pain up to 11 wk after continuous ketamine infusion
Finch et al.[34]	Randomized, double-blind, crossover, placebo-controlled	CRPS I (n=18); CRPS II (n=2), duration of pain from 2 mo to 19.2 y	20 (14 F)	Ketamine 10% in PLO cream or PLO cream without ketamine; 0.5 mL of one cream applied to symptomatic limb and 0.5 mL of other cream applied to healthy limb	Light touch using pressure pain threshold, punctate stimulation, light brushing, thermal stimuli (performed for the symptomatic and contralateral limb and on either side of forehead)	Two separate trials 1 wk between, sensory assessments performed 30 min before and after application	No effect on pain in either group, ketamine cream inhibited allodynia to lightly brushing of the symptomatic limb	None	Topical ketamine does not reduce pain. Could be used as an adjunct to sensory motor retraining programmes
Kiefer et al.[41]	Prospective, open-label, pilot	Average pain intensity >70 mm on a 100 mm VAS, failed other treatments	4 (4 F)	Titrated ketamine infusions (50–500 mg/d)	VAS, mechanosensory detection threshold, mechanosensory pain thresholds,	10 d period	No reduction of pain, no effect on thermo- and mechanical detection or pain thresholds,	None	Ketamine can be gradually titrated to large dosages (500 mg/d) without

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Table VII. Contd

Study	Study type	Patient selection	No. of patients	Intervention	Assessment tools	Assessment intervals	Results	Adverse effects	Conclusions
					temperature detection thresholds, thermal pain thresholds		lack of therapeutic response in first four patients led to termination of study		clinically relevant adverse effects. Ineffective for pain. Not recommended
Kiefer et al.[45]	Phase II, nonrandomized, open-label	CRPS based on IASP criteria, modified research diagnostic CRPS criteria and Budapest criteria, daily pain >7 over 6 mo standard therapy, failed conventional therapy	20 (18 F)	IV ketamine over 5 d at 3 mg/kg/h with gradual titration up to final dose of 7 mg/kg/h in ICU; IV clonidine minimum dose of 0.15 μg/kg/h; adjuvant midazolam	NRS, movement disorder, extremity motor evaluation, quality of life, ADLs, social integration, ability to work	Baseline; 1 wk; 1, 3 and 6 mo	Significant pain relief at 1 wk in entire group, pain relief in CRPS subgroup maintained at 3 and 6 mo. Improvement in quality of life and ability to work, long-term pain relief observed in 50% of patients	No major life-threatening complications reported	Suggests benefit in pain reduction at 3 and 6 mo in previously refractory CRPS patients
Koffler et al.[47]	Observational, prospective	Met IASP diagnostic and modified research criteria for CRPS I, pain intensity >6 (Likert scale) for >6 mo, failed conventional therapy	9 (8 F)	Maintained IV ketamine plasma concentrations of 250–300 μg/dL for at least 4.5 d (medically induced coma)	MPQ WAIS-III subtests: Information and Vocabulary, Digit Span, Digit Symbol Coding, Story I or II of the Logical Memory subtest from WMS-III, BDI, MMPI-2	6 wk follow-up	Significant reduction in overall pain after treatment, significant improvement in brief attention and thought processing speed and other cognitive domains, lack of improvement in depression and anxiety	No adverse neurocognitive effects, mild decline in motor strength	Deep ketamine therapy is effective in CRPS I
Goldberg et al.[43]	Open-label, prospective	CRPS diagnosis based on IASP criteria	40 (36 F)	10 d outpatient ketamine infusion of 40–80 mg lasting 4 h, increased over 10 d to 80 mg; patients also received clonidine 0.1 mg prior	Pain diaries for each d prior to the infusion; verbal analogue pain scale; affective	10 d during infusion	Significant reduction in pain intensity from initiation to d 10, significant functional	None	Significant reduction of pain with functional improvement and a tendency to decreased

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Table VII. Contd

Study	Study type	Patient selection	No. of patients	Intervention	Assessment tools	Assessment intervals	Results	Adverse effects	Conclusions
				to infusion, as well as midazolam	components of pain		improvement by d 10		autonomic dysregulation. No long-term follow-up reported
Correll et al.[44]	Observational, retrospective	CRPS diagnosis based on presence of sensorimotor and autonomic disturbances in affected limb	33 (8 F)	IV ketamine infusion started at 10 mg/h and titrated to analgesia to 50 mg/h (max) over 4.7 d; some patients received second infusion	NRS	At 3 mo, 6 mo, 1 y and 3 y	After first treatment, 54% of 33 patients pain free at 3 mo and 31% pain free at 6 mo, after a repeat ketamine infusion, 58% of 12 patients had pain relief for 1 y and 33% remained pain free at >3 y	Elevated LFTs that normalized after discontinuation of ketamine, CNS effects, such as a feeling of inebriation, hallucinations, dizziness, blurred vision and nausea	IV ketamine may offer a promising therapeutic option in the treatment of CRPS
Sigtermans et al.[42]	Observational, prospective	CRPS I based on IASP criteria VAS pain score >5	10 (10 F)	IV ketamine infusions with increasing doses at 20 min intervals	Baseline pain ratings, VAS to heat stimuli during infusion and for 3 h post-infusion	3 h post-infusion	Significant VAS reduction at end of infusion, analgesia persisted beyond the infusion period when measured plasma ketamine concentrations were low	None reported	Ketamine affected pain more than that of the experimental pain for 3 h beyond the infusion period. Analgesic effect lasted even at low serum concentration of ketamine
Goldberg et al.[46]	Observational, prospective	CRPS based on IASP criteria	16 (F not stated)	IV ketamine titrated from 10 to 40 mg/h and maintained for 5 d; transdermal clonidine 0.1 mg/d; midazolam 2–4 mg	NRS	5 d during infusion	Significant pain relief by d 2 of infusion that correlated with the max plasma concentrations of ketamine and norketamine	No significant adverse effects	Minimal pain relief on d 1 followed by significant relief by d 3. No longer-term follow-up

ADLs = activities of daily living; **BDI** = Beck Depression Inventory; **F** = females; **IASP** = International Association for the Study of Pain; **ICU** = intensive care unit; **IV** = intravenous; **LFT** = liver function test; **max** = maximum; **MMPI-2** = Minnesota Multiphasic Personality Inventory 2; **MPQ** = McGill Pain Questionnaire; **NRS** = numerical rating scale; **NS** = normal saline; **PLO** = pluronic lecithin organogel; **QLQ** = Quality of Life Questionnaire; **RASQ** = Radboud Skills Questionnaire; **VAS** = visual analogue scale; **WAIS-III** = Wechsler Adult Intelligence Scale III; **WMS-III** = Wechsler Memory Scale-III; **WAQ** = walking ability questionnaire.

Table VIII. Case studies on the use of ketamine in the treatment of complex regional pain syndrome (CRPS)

Reference	Study type	Patient selection	No. of patients	Intervention	Assessment tools	Results	Adverse effects	Conclusions
Sunder et al.[40]	Case study	CRPS II	3	IV ketamine as adjuvant to sympathetic blocks in unspecified dose	VAS, heat allodynia, mechano-allodynia	Marked decrease in thermal and 'vicarious' allodynia	None	Ketamine has role in patients with debilitating heat allodynia, variable doses and routes of administration reported
Villanueva-Perez et al.[50]	Case report	CRPS I	1	Oral ketamine 30 mg q8h, increasing weekly in 5 mg increments to max of 60 mg q6h	VAS	Reduction in VAS over 4–5 mo	Nausea, vomiting	Oral ketamine syrup had long-term effects
Kiefer et al.[51]	Case report	CRPS I	1	IV ketamine 3–5 mg/kg/h, gradually increasing over 5 d	VAS	Effect seen at d 2 and complete resolution of symptoms by d 6, patient had complete remission from CRPS for 8 y	NR	Ketamine is effective in patients with generalized, refractory CRPS
Becerra et al.[52]	Case report	CRPS	1	Bolus IV ketamine 1.5 mg/kg and midazolam 7.5 mg while in ICU; maintained by ketamine infusion over 5 d starting at 3 mg/kg/h, increased daily to 7 mg/kg/h	VAS, spontaneous and evoked pain levels, stimuli tests	Pain decreased from 7/10 to 0–1/10	NR	Ketamine is effective in the treatment of CRPS followed by fMRI changes
Shirani et al.[53]	Case report	CRPS I	1	IV ketamine 50 mg over 30 min followed by two more infusions 1 wk apart, midazolam as adjuvant	NRS	Oedema, discoloration and temperature of the affected areas normalized, patient was pain free at end of third treatment	Migraine	Early treatment with ketamine may be beneficial, ketamine was effective after 6 y of ineffective long-term therapy with other drugs
Everett et al.[54]	Case report	CRPS I	1	IV ketamine infusion titrated to 0.6 mg/kg/h (max) and peripheral nerve ropivacaine infusion	VAS	Pain decreased to 0/10, full range of motion	None	Ketamine and ropivacaine effective in treatment of CRPS
Nama et al.[55]	Case report	CRPS	1	IV ketamine infusion (100 μg/kg/h) and dexmedetomidine for 19 h	NRS	Pain 0/10 at end of infusion	None	Ketamine and dexmedetomidine effective in CRPS
Harbut and Correll[56]	Case report	CRPS	1	IV ketamine infusion initiated at 10 mg/h and increased to 30 mg/h (max)	VAS	Patient remained pain free at d 4 and at 5 mo follow-up	Feelings of inebriation, mild elevation of BP	Ketamine effective in treatment of CRPS
Ushida et al.[57]	Case series	CRPS	7 (CRPS II = 2; CRPS I = 5)	Topical ketamine (0.25–1.5%) applied to affected limbs	VAS	Decreased VAS scores in four patients with early dystrophic stage of CRPS I	None	Topical ketamine effective in early stages of CRPS I

fMRI = functional MRI; **ICU** = intensive care unit; **IV** = intravenous; **max** = maximum; **NR** = not reported; **NRS** = numerical rating scale; **q6h** = every 6 hours; **q8h** = every 8 hours; **VAS** = visual analogue scale.

tomimetic effects and headaches.[38,39,44,47] Hypertension and elevated liver enzymes were other reported adverse effects that resolved after termination of the ketamine infusion.[44,53] In the study by Koffler et al.,[47] the cognitive effects of ketamine were extensively evaluated with a battery of neuropsychological tests prior to infusion and at 6 weeks post-infusion. Their conclusion was that ketamine has no residual cognitive effects at 6 weeks.

3.5 Use of Adjuvants

In several studies that did not report psychotomimetic effects and that did not use feelings of inebriation as endpoints for ketamine dose titrations, adjuncts such as clonidine or midazolam were used.[39,43,45,46,53] In one case study, it was documented that ketamine-induced hypertension improved with the use of midazolam.[53]

4. Conclusion

In treating the many possible disease mechanisms of CRPS, multiple receptors and physiological pathways have been targeted, including neuropeptides, inflammatory markers and other regulators.[3] Ketamine has been studied frequently because of its potential ability to alter the central sensitization noted in chronic pain states.

There are multiple difficulties encountered when attempting to compare the different studies using ketamine. Various investigators have used different doses, different routes of administration and different outcome measures. The studies published to date contain relatively small sample sizes. Perhaps most significantly, most of the articles used the original broad IASP definition of CRPS, not the more specific Budapest criteria.

In this review, both prospective and retrospective studies representing multiple routes of ketamine administration were included in an attempt to give the broadest possible view of literature support for the role of ketamine in treating CRPS.[34,39,58] Although observational studies do not provide as high a level of evidence as randomized controlled trials, their inclusion and review in this article bridges gaps in our understanding of the potential benefits of ketamine in the treatment of CRPS and helps to establish its safety and appropriate route of administration.[35] To date, there have been nine case studies/reports published using ketamine to control CRPS. These nine reported cases and case series show that ketamine is effective in treating CRPS; however, unsuccessful trials may be underreported in the literature because of reporting bias. Without having data regarding unsuccessful trials it is difficult to gauge the efficacy of ketamine for the treatment of CRPS.

The current level of evidence is 2B (i.e. weak recommendation, moderate-quality evidence) for the use of ketamine in the treatment of CRPS pain. We do not have sufficient evidence to recommend routine use of ketamine in CRPS. Within the context of this limited evidence for use of ketamine, there are limited data about the optimal dose, route and timing of administration. Although ketamine demonstrates promise for safe and effective use in the treatment of CRPS, the need for large, well designed, randomized controlled trials is evident.

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