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Ketamine for Complex Regional Pain Syndrome: A Narrative Review Highlighting Dosing Practices and Treatment Response

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a frequently debilitating pain condition affecting one or more limbs, which can develop with or without known trauma to the peripheral nervous system. CRPS has been described under other names, such as Sudeck's atrophy, algodystrophy, causalgia, and reflex sympathetic dystrophy.[1] Individuals with CRPS develop a constellation of signs and symptoms characterized by autonomic and neuroinflammatory changes, such as redness and swelling, which can vary over time.[2]

The International Association of Pain (IASP) maintains the most up-to-date diagnostic criteria ("Budapest criteria") for CRPS.[3] The IASP also distinguishes between 3 subtypes: CRPS I ("type I"), which occurs without a known peripheral nerve lesion; CRPS II ("type II"), which is attributable to a discrete peripheral nerve lesion; and CRPS with remission of some features, which refers to patients who previously met full diagnostic criteria but no longer meet them.[4] For the purposes of this review, the authors address all 3 subtypes under the general term "CRPS."

The incidence of CRPS in a general population ranges from 5.5 to 20.6 per 100,000 person-years,[5,6] comparable to the incidence of trigeminal neuralgia.[7] Although CRPS accounts for only 1.2% of all pain diagnoses made in the United States,[8] the associated financial burden and amount of disability can be substantial. The mean lifetime medical costs of having CRPS is estimated to be $171,153 to $229,624 depending on therapy received.[9] In a cross-sectional study of patients with CRPS, 81% had stopped work owing to pain.[10]

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CONFLICTS OF INTEREST

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Disease duration can be quite long; a quarter of patients presenting to a pain clinic with CRPS might report at least 10 years of symptoms.[10]

Only 2 treatments have been approved for CRPS by the Food and Drug Administration: spinal cord stimulation (SCS) and dorsal root ganglion (DRG) stimulation.[11,12] One randomized controlled trial (RCT) for SCS in patients with CRPS found that it is effective for pain reduction; however, its advantage over physical therapy alone is lost 5 years after implantation.[13,14] A comparative effectiveness trial between SCS and DRG stimulation found that the proportion of patients with CRPS who reported pain relief at 12 months was higher in the DRG arm compared with the SCS arm.[15] However, much like SCS, the benefits of DRG stimulation are not experienced by all patients, or the effects tend to wane after a few years. In a longitudinal study of patients who received DRG stimulators for chronic intractable pain, 19% experienced no pain relief during the trial, and 10% had explants within the first 24 months owing to inadequate pain relief or the device could not provide enough current to maintain relief; 17% of the original cohort had later explants owing to inadequate pain relief or lead migration within 7 years of implantation.[16] Additional treatments for CRPS are needed, particularly for patients who have failed neuromodulation therapies.

EVIDENCE FOR KETAMINE IN COMPLEX REGIONAL PAIN SYNDROME

In this narrative review, the authors have included a summary table of retrospective and prospective studies involving the use of intravenous (IV) ketamine in patients with CRPS (Table 1), with a focus on dosages and response rates. They have excluded case reports and studies with mixed populations that include patients with non-CRPS pain conditions. Although intravenous ketamine has been described as a potential treatment for CRPS since the mid-1990s,[17] only 2 randomized placebo-controlled trials have tested ketamine in patients with CRPS. Schwartzman and colleagues[18] in the United States demonstrated that a 10-day series of outpatient subanesthetic infusions can result in superior analgesia for up to 12 weeks, compared with placebo infusions. Sigtermans and colleagues,[19] located in the Netherlands, showed that a 5-day continuous subanesthetic infusion delivered in an inpatient setting also showed analgesic superiority compared with placebo for up to 11 weeks.

Overall, the evidence for ketamine infusions in CRPS remains modest. A 2013 Cochrane review concluded that ketamine infusions had low-quality evidence backing its use, similar to the level of evidence for bisphosphonates, calcitonin, graded motor imagery, mirror therapy, and CRPS-focused physical and occupational therapy.[20] For context, many oral medications commonly used in CRPS—such as opioids, antidepressants, and antiepileptics—are not supported by randomized studies in CRPS. A more recent review authored by the American Society of Regional Anesthesia and Pain Medicine (ASRA), American Academy of Pain Medicine (AAPM), and the American Society of Anesthesiologists (ASA) argued that the use of intravenous ketamine in CRPS had grade B evidence, corresponding to low to moderate certainty.[21] A recent meta-analysis found that the available clinical evidence supports ketamine as a treatment for CRPS, although the investigators identified high heterogeneity between studies and high risk of publication bias.[22]

BRIEF OVERVIEW OF KETAMINE'S ANALGESIC MECHANISMS

Considering that the context-sensitive half-time of ketamine plateaus at around 1 hour,[23] it is remarkable that the analgesic effects of a prolonged ketamine infusion can last several weeks to months. The physiologic mechanism of ketamine's analgesic effect in CRPS is not well understood, although several mechanisms have been proposed.

First, ketamine is primarily known as an antagonist of the N-methyl-D-aspartate (NMDA) receptor, an excitatory glutamatergic ion channel expressed by neurons. NMDA receptors are necessary for long-term potentiation, a process by which neurons strengthen and increase signal transmission between each other with repetitive stimulation.[24] Long-term potentiation is thought to be a major mechanism underlying hyperalgesia, allodynia, and central sensitization,[25,26] which are seen frequently in CRPS; ketamine's antagonism of NMDA receptors is thought to reverse these phenomena.[27,28] The analgesic mechanism of action of ketamine may be much more complex, however, given that ketamine also interacts with several other receptors, including opioid, gamma-aminobutyric acid, dopamine, muscarinic, nicotinic, and L-type calcium channels.[29]

Neuroimmune modulation has also been proposed as a mechanism underlying ketamine's efficacy in CRPS. Inflammatory symptoms are a distinguishing feature of CRPS, especially in the acute stage. Patients with CRPS show changes in several immunologic markers within their cerebrospinal fluid,[30] indicating neuroinflammatory changes in the central nervous system as well. NDMA receptors are found on microglia and astrocytes, which are the immune cells of the central nervous system, and are thought to mediate the analgesic effects of ketamine on neuropathic pain.[31,32] Ketamine also exerts a variety of effects on peripheral markers of inflammation.[33] Ketamine can rapidly suppress proinflammatory cytokines in a variety of clinical populations, from patients undergoing major surgery[34,35] to patients with treatment-resistant depression with or without chronic pain.[36,37] Ketamine's complex effects on the neuroimmune system may in part explain ketamine's analgesic effects in CRPS.

The antidepressant effect of ketamine is well-documented in the psychiatric literature,[38] suggesting that ketamine may also impact the affective aspects of CRPS. Chronic pain and depression are known to be highly comorbid,[39,40] and there appears to be a bidirectional relationship between depression and pain severity.[41] In patients with CRPS, disability and pain severity were more strongly associated with anxiety and depression, in comparison to patients with low back pain.[42] Functional neuroimaging studies have found that ketamine exerts its effects in cortical areas that are similar between patients with major depressive disorder and CRPS. In depressed patients without chronic pain, ketamine increases the activity of the anterior cingulate gyrus and medial prefrontal cortex.[43] One functional magnetic resonance imaging study comparing a patient with CRPS with healthy subjects found evidence of post-ketamine normalization of resting state network activity in the anterior cingulate gyrus and prefrontal cortex.[44] The antidepressant effects of ketamine are thought to be mediated by a variety of mechanisms, including a glutamatergic surge associated with increased brain-derived neurotrophic factor, anti-inflammatory changes, and opioid receptor agonism.[45] Interestingly, the Sigtermans trial did not find changes in anxiety or depression in patients who received ketamine, whereas the Schwartzman trial did reveal

significant decreases in the affective component of pain after ketamine infusion.[18,19] These differences may have arose from their different methods of measuring the emotional impact of pain.

KETAMINE DOSAGE AND DURATION OF PAIN RELIEF

To date, no randomized dose-ranging studies have been conducted for ketamine infusion therapy in patients with CRPS, or in any chronic pain condition. Several investigators have noted that, when comparing studies across all chronic pain conditions, the total dose of ketamine appears correlated with the duration of pain relief—with larger total doses resulting in longer-lasting analgesia.[21,46-48] In patients with fibromyalgia and chronic neuropathic pain, brief subanesthetic infusions (0.5 mg/kg over 30 minutes or 2 hours, respectively) do not produce analgesia lasting beyond 1 week.[49,50] Conversely, high-dose "ketamine comas" have been described in a series of 20 patients with CRPS who received a 5-day anesthetic ketamine infusion (up to 7 mg/kg/h), which required intubation and mechanical ventilation. Some patients experienced extraordinary results from this high-dose protocol, with about 50% of patients remaining completely pain-free for 5 to 11 years. Drawbacks of this approach include the high cost of intensive care and a high rate (20%) of iatrogenic complications, such as urinary and pulmonary infections.[51]

Not surprisingly, intermediate doses of intravenous ketamine have yielded intermediate lengths of pain relief. The RCTs conducted by Sigtermans and Schwartzman, separately, used similar subanesthetic infusion rates of ketamine, which were gradually raised over a few days. The Sigtermans trial started their infusions at 0.071 mg/kg/h and titrated the infusion rate 3 times daily up to 0.42 mg/kg/h, for an average of 4.2 continuous infusion days.[19] The Schwartzman trial initiated their ketamine infusions at 0.175 mg/kg/h on day 1, increased to 0.26 mg/kg/h on day 2, and reached their maximum dose of 0.35 mg/kg/h on day 3, and continued administering this dose 4 hours per day, for a total of 10 days.[18] Both studies demonstrated that a subanesthetic, multiday infusion regimen can yield 11 to 12 weeks of pain relief.

These intermediate doses of ketamine appear to be reflected in clinical practice as well. In a consensus survey of French pain physicians who are considered experts in ketamine therapy, the preferred dose of intravenous ketamine was 0.5 to 0.9 mg/kg per day, for 4 days of treatment.[52] Similarly, in a nationwide survey of pain clinics in the Netherlands, the median starting dose of intravenous ketamine in the outpatient setting was 5 mg/h; the median maximum dose was 27.5 mg/h, and the median infusion duration was 6 hours per day. The median starting dose in the inpatient setting was 5 mg/h; the median maximum dose was 25 mg/h, and the median days of infusion was 4 days.[53]

It is interesting to note that the Schwartzman trial infused ketamine for a total of 40 hours, whereas the Sigtermans trial infused ketamine for approximately 100 hours. Despite the Schwartzman trial having less than half the infusion hours with comparable infusion rates, the duration of pain relief obtained was similar to that of the Sigtermans trial. This might be attributed to the Schwartzman trial administering clonidine before and after each infusion; the investigators acknowledged that clonidine has been shown to potentiate

the analgesic effects of ketamine.[54] An alternative explanation is that repeating multiple ketamine infusions in close succession, with daily breaks, might produce longer-lasting analgesia, compared with one continuous multiday infusion. More research into the optimal infusion regimen for intravenous ketamine is needed.

Based on the available data, an optimal balance of efficacy, cost, and safety likely lies between a single-day subanesthetic infusion (noneffective beyond 1 week) and a multiday anesthetic coma (high cost and high complication rate). Recent consensus guidelines from ASRA, AAPM, and ASA recommend starting with an outpatient infusion protocol that delivers a minimum dose of 80 mg infused over 2 hours or longer, and reassessing the patient before extending treatment.[21] Further dose-ranging studies will be necessary to establish an ideal dosing protocol.

RESPONSE RATE AND PREDICTORS OF KETAMINE RESPONSE

Researchers and clinicians have observed that the analgesic response to intravenous ketamine is highly variable.[55] In studies that report the percentage of treatment responders to ketamine, approximately one-half of patients with CRPS achieve some definition of long-term response to ketamine infusions. In a retrospective study of inpatients with CRPS who received a continuous subanesthetic ketamine infusion (3-14 mg/h, or 0.04-0.2 mg/kg/h for a 70-kg person) for up to 7 days, responders were defined as having at least a 2-point reduction in pain score on the 0 to 10 Numeric Rating Scale; in this study, 48% were still considered “responders” at 30 days postinfusion.[56] In the high-dose, open-label anesthetic infusion (3-7 mg/kg/h) study by Kiefer and colleagues,[51] 50% of participants experienced 5 to 11 years of complete pain relief.

Despite knowing such response variability exists, there are currently no well-established, replicated predictors of treatment response. In the 2 placebo-controlled RCTs for ketamine in CRPS, the investigators noted that the duration of disease did not correlate with analgesic response, which suggests that ketamine may remain a viable treatment even for patients with highly chronic, protracted disease.[18,19]

Various experimental biomarkers of ketamine response have been reported. Bosma and colleagues[57] explored whether quantitative sensory testing and functional neuroimaging could predict analgesic response to ketamine in patients with neuropathic pain; they found that treatment responders exhibited, at baseline, greater temporal summation of pain and increased dynamic functional connectivity between areas of the brain involved in the descending nociceptive pathway. The investigators proposed that dynamic functional connectivity mediates the relationship between temporal summation of pain and analgesic response to ketamine. From a practical standpoint, however, it may be more feasible to explore temporal summation of pain as a method of predicting treatment response to ketamine infusions in clinical populations.

Genomic markers have also been explored as potential predictors of ketamine response. In patients with CRPS, nonresponders to ketamine were found to have lower baseline levels of a specific microRNA (miR-548d-5p), which the investigators propose might

increase glucuronosyltransferase activity, increasing levels of inactive conjugates, and thus potentially reducing the therapeutic efficacy of ketamine.[58]

Additional insights may be gleaned from studies of ketamine in major depressive disorder. In these studies, the most replicated predictors for the antidepressant response to ketamine include a family history of alcohol dependence and higher body mass index.[59] Increased heart rate and heart rate variation during ketamine infusion have also shown discriminative ability for predicting antidepressant response[60]—perhaps as a surrogate marker of increased physiologic sensitivity to ketamine's effects on the autonomic nervous system.

NONINJECTABLE FORMULATIONS OF KETAMINE

Oral and intranasal are the 2 most common nonparenteral routes of ketamine used.[16,56,57] The bioavailability is limited to less than 20% via the oral route owing to extensive hepatic metabolism.[58] Norketamine is the ketamine's metabolite formed via hepatic demethylation. It is 33% as potent as ketamine, has a longer half-life than ketamine (4 hours vs 2-3 hours), and is thought to contribute to oral ketamine's analgesic potential.[59,60,61] Some studies have reported successful long-term use of oral ketamine (>3 months) with a dosage ranging from 0.5 to 3 mg/kg in 3 to 4 divided dosages per day.[62,63] However, long-term use of ketamine needs to be under close supervision, with the eventual goal of discontinuation given the abuse potential and adverse effects associated with chronic use seen in ketamine abusers (cognitive impairment, ureteric metaplasia, and hepatic toxicity).[64,65]

The intranasal route has a higher bioavailability (up to 50%), as it avoids hepatic first-pass metabolism with absorption via the highly permeable and vascular nasal mucosa.[66,67] Most of the studies for the use of intranasal ketamine (usually 10-50 mg per spray, up to 1 mg/kg) for pain have been for intractable cancer pain, breakthrough pain, acute pain in the emergency room setting, or procedural sedation, especially in the pediatric population.[67-74] Recently published, multisociety consensus guidelines on the use of ketamine for chronic pain recommend that oral formulation can be used in lieu of serial infusion in those who respond positively to intravenous ketamine (grade B recommendation, low level of certainty). The guidelines also found moderate evidence (grade B recommendation, moderate level of certainty) for the use of intranasal ketamine preparation for breakthrough pain.

SUMMARY

CRPS is a frequently debilitating chronic pain condition with few evidence-based treatment options, and many patients with CRPS have intractable symptoms prompting the need for novel therapies. Intravenous ketamine has been investigated as a potential treatment for CRPS for over 20 years, with low to moderate levels of evidence. Current recommendations for initial ketamine dosing are to infuse at least 80 mg over a period of 2 hours or longer.[21] In addition, the current literature suggests that approximately one-half of patients with CRPS will experience long-term pain relief from a single ketamine infusion—although reliable predictors of treatment response are still unknown. Additional studies are needed to (1) identify doses and infusion protocols that strike an optimal balance between efficacy, cost,

and safety; and (2) identify predictors of long-term analgesic response, in order to maximize the chance of treatment success in carefully selected patients.

DISCLOSURES

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KEY POINTS

- Intravenous ketamine at subanesthetic doses can produce long-lasting, but not permanent, pain relief in patients with complex regional pain syndrome.
- Clinical evidence across a variety of chronic pain conditions suggests that larger total doses of ketamine are correlated with longer periods of pain relief. However, very-high-dose infusions are often limited by financial cost and adverse effects.
- Subanesthetic doses (0.10–0.9 mg/kg/h) of intravenous ketamine given continuously over 5 days is the most commonly studied infusion regimen for complex regional pain syndrome and is most commonly reflected in clinical practice.
- Not all patients experience long-term (>1–3 months) pain relief from ketamine infusions; there appear to be responders and nonresponders to intravenous ketamine therapy.
- Further research is needed to identify the optimal dose and infusion protocol for intravenous ketamine, the utility of nonintravenous routes, as well as predictors of long-term response.

CLINICS CARE POINTS

- Duration of complex regional pain syndrome has not been shown to affect analgesic response rates to ketamine infusion. Even patients with highly chronic complex regional pain syndrome refractory to other therapies should be considered for ketamine infusion. Conversely, ketamine may also be considered in patients with relatively acute presentations of complex regional pain syndrome.
- Meaningful pain relief lasting 1 to 3 months can be expected in 20% to 65% of patients with complex regional pain syndrome after a single ketamine infusion, if adequately dosed.
- The most studied ketamine infusion regimen is a subanesthetic dose (0.10–0.9 mg/kg/h) administered in a monitored inpatient setting over 5 consecutive days. Start at a lower dose and gradually uptitrate until analgesia is attained, or when adverse effects limit dose increases.
- Up to 10 days of outpatient infusions may be required to obtain a similar analgesic duration as 5 days of inpatient infusions; however, the ideal number of infusion days is unknown.
- With the first infusion, aim to give a total dose of at least 80 mg over a period of 2 hours or longer, as recommended by the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists.
- Assess patient response before repeating or lengthening treatment duration.
- Premedication or coadministration of intravenous midazolam (2–4 mg) and oral clonidine (0.1 mg) may be considered to limit the dissociative and sympathomimetic side effects of ketamine.

Table 1

Characteristics of intravenous ketamine studies in patients with complex regional pain syndrome (primary analyses only)

Study and Year	Study Design	Sample Size	Setting	Drug	Infusion Rate	Treatment Duration, d	Duration of Pain Relief	Percent Responders	Definition of Responder	Medications to Control Side Effects
Correll et al, [75] 2004	Retrospective chart review	33	Inpatient	Racemic ketamine	10–50 mg/h	4.7	9.44 mo (mean duration of being pain free)	54	“Pain free” for ≥3 mo	Not reported
Goebel et al, [76] 2015	Open-label single-arm study	5	Inpatient	Racemic ketamine	0.15–0.9 mg/kg/h	5	6.7 wk (mean duration of “meaningful” pain relief)	20	“Meaningful” relief at 3 mo	Not reported
Goldberg et al, [77] 2010	Open-label single-arm study	16	Inpatient	Racemic ketamine	10–40 mg/h	5	—	60	“Meaningful pain relief” at 3 mo	Midazolam 2–4 mg intravenous (IV) q4h for restlessness, dysphoria, or hallucination, transdermal clonidine 0.1 mg/day
Kiefer et al, [51] 2008	Open-label single-arm study	20	Inpatient (intensive care)	Racemic ketamine	3–7 mg/kg/h	5	—	65	"Full remission" at 3 mo	Midazolam 0.15–0.4 mg/kg/h IV, clonidine 0.2–0.85 μg/kg/h IV
Mangnus et al, [56] 2021	Retrospective chart review	48	Inpatient	S(+)-ketamine	3–14 mg/h	7	—	48	Reduction of ≥2 points on the 0–10 Numeric Rating Scale pain scale at first follow-up (median 4 wk)	None (ketamine dose was reduced until side effects abated)
Schwartzman et al, [18] 2009	Randomized placebo-controlled trial	26	Out patient	Racemic ketamine	0.175–0.35 mg/kg/h	10	Up to 12 mo (significant decrease compared with placebo)	—	—	Midazolam 2 mg IV before and after infusion, clonidine 0.1 mg PO before infusion
Sigtermans et al, [19] 2009	Randomized placebo-controlled trial	60	Inpatient	S(+)-ketamine	0.072–0.432 mg/kg/h	4.2	11 wk (significant decrease compared with placebo)	—	—	None (ketamine dose was reduced until side effects abated)