PAIN MEDICINE
Volume 5 • Number 3 • 2004

Subanesthetic Ketamine Infusion Therapy: A Retrospective Analysis of a Novel Therapeutic Approach to Complex Regional Pain Syndrome

Graeme E. Correll, BE, MBBS, FANZCA,* Jahangir Maleki, MD, PhD,† Edward J. Gracely, PhD,‡ Jesse J. Muir, MD,§ and Ronald E. Harbut, MD, PhD¶

*Anaesthetics Department, Mackay Base Hospital, Mackay, Queensland, Australia; †Drexel University College of Medicine, Medical College of Pennsylvania Hospital, Philadelphia, Pennsylvania; ‡Department of Family, Community, and Preventive Medicine, Drexel University College of Medicine, Philadelphia, Pennsylvania; §Department of Anesthesiology, Mayo Clinic Scottsdale, Scottsdale, Arizona; ¶Department of Anesthesiology, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania

ABSTRACT

Complex Regional Pain Syndrome (CRPS) is a disorder that can be accompanied by severe pain that is often both chronic and resistant to conventional therapy. Harbut and Correll previously reported the successful treatment of a 9-year case of intractable Type I CRPS with an intravenous inpatient infusion of ketamine in an adult female patient [1].

Objective. The purpose of this study was to ascertain if indeed the use of subanesthetic inpatient infusions of ketamine provide meaningful improvements in pain scores, and thus, quality of life, in patients suffering from CRPS. To achieve this objective we focused our analysis on the relief of pain obtained by patients undergoing this novel treatment option developed at Mackay Base Hospital, Queensland, Australia.

Methods. Case notes of 33 patients whose CRPS pain was treated by the inpatient administration of a continuous subanesthetic intravenous infusion of ketamine were reviewed. The dose and duration of ketamine therapy and the degree and duration of relief obtained were recorded. Notable side effects were also recorded. The degree of relief obtained (immediately after the infusion) was assessed using pre- and posttreatment numeric pain scores. The duration of relief obtained (throughout the follow-up period) was analyzed using a Kaplan-Meier cumulative survival curve analysis.

Results. A total of 33 patients with diagnoses of CRPS who had undergone ketamine treatment at least once were identified. Due to relapse, 12 of 33 patients received a second course of therapy, and two of 33 patients received a third. The degree of relief obtained following the initial course of therapy was impressive (N = 33); there was complete pain relief in 25 (76%), partial relief in six (18%), and no relief in two (6%) patients. The degree of relief obtained following repeat therapy (N = 12) appeared even better, as all 12 patients who received second courses of treatment experienced complete relief of their CRPS pain. The duration of relief was also impressive, as was the difference between the duration of relief obtained after the first and after the second courses of therapy. In this respect, following the first course of therapy, 54% of 33 individuals remained pain free for ≥3 months and 31% remained pain free for ≥6 months. After the second infusion, 58% of 12 patients experienced relief for ≥1 year, while almost 33% remained pain free for >3 years. The most frequent side effect observed in patients receiving this treatment was a feeling of inebriation. Hallucinations occurred in six patients. Less frequent side effects also included complaints of lightheadedness, dizziness, and nausea. In four patients, an alteration in hepatic enzyme profile was noted; the infusion was terminated and the abnormality resolved thereafter.

Reprint requests to: Ronald E. Harbut, M.D., Ph.D., Department of Anesthesiology, H187, Penn State Milton S. Hershey Medical Center, 500 University Drive, Hershey, Pennsylvania 17033. Tel: (717) 531-5680; Fax: (717) 531-4204; Jahangir Maleki, MD, PhD, Drexel University College of Medicine, Medical College of Pennsylvania Hospital, 3300 Henry Avenue, Philadelphia, PA 19129. Tel: (215) 842-7335; Fax: (215) 843-4467.

 1526-2375/04/$15.00/263 263–275

Conclusion. This retrospective review suggests that limited subanesthetic inpatient infusions of ketamine may offer a promising therapeutic option in the treatment of appropriately selected patients with intractable CRPS. More study is needed to further establish the safety and efficacy of this novel approach.

Key Words. Alpha-2-Adrenergic Agonist; Central Sensitization; Complex Regional Pain Syndrome; Ketamine; Neuropathic Pain; Noncompetitive NMDA Receptor Antagonist

Introduction

The treatment of Complex Regional Pain Syndrome (CRPS) can be a very frustrating experience for both patient and practitioner, as it is often resistant to a variety of conventional therapies. The modulation of pain processing with medications such as antidepressants, antiepileptics, opioids, and membrane-stabilizing compounds often produces only modest therapeutic benefits.

Windup and central sensitization are key neurologic processes that appear to be involved in the induction and maintenance of CRPS/neuropathic pain [2–9]. Because overexcitation of the N-methyl-D-Aspartate (NMDA) receptor complex appears to play a major role in the development of these phenomena, there have been efforts made by many for over 20 years to treat both chronic as well as postoperative pain using NMDA receptor antagonists [10–26]. It has been hoped that such an approach might help prevent and/or even reverse the unbearable increases in pain (intensity and spread) that many patients experience after trauma or surgery.

While animal experiments have shown evidence that NMDA receptor antagonists can inhibit sensitization, the clinical usefulness of these findings has been limited due to a lack of meaningful efficacy and/or excessive side effects. Interpretation of clinical reports of ketamine use in pain practice is further complicated when different routes of administration are used.

The reasons for a previous lack of durable efficacy of NMDA antagonists in human chronic pain studies are many. Human pain syndromes are mechanistically more complex than animal models. The multiplicity of neuropathic pain phenomena [27] prevents the identification of a homogeneous patient sample and the application of a standardized drug-testing methodology in clinical practice. All of this is further complicated by the lack of an NMDA antagonist that delivers a good measure of efficacy, tolerability, and clinical safety. Drugs such as dextromethorphan, amantadine, and memantine, although relatively safe (from a central nervous system [CNS] side effect standpoint), have relatively weak NMDA receptor-inhibition activity and appear to have a low potential for blocking the sensitization process. Ketamine (on the other hand) has more potent NMDA receptor-blocking properties, but might also produce more CNS side effects.

Due to its potential for CNS side effects, ketamine has been limited to the practice of anesthesiology, where a high bolus dose of intravenous ketamine clearly alters mental status and induces general anesthesia. In pain medicine over the last 20 years, lower bolus doses of ketamine have failed to provide any meaningful (i.e., durable) analgesia in chronic pain states. Likewise, various continuous-infusion approaches have been tried in the hopes that they might show durable analgesic benefit (see above). In many of the above cases, evanescent relief or unwanted CNS side effects have limited the beneficial responses observed.

It is possible that a more successful approach to desensitization therapy using an NMDA antagonist such as ketamine requires a more individualized stepwise tailoring of the dosage (i.e., infusion rate) and duration of drug administration. Furthermore, such desensitization therapy may require repeat treatment cycles in some patients (who initially respond with meaningful relief) to maintain the desired desensitization effect, particularly if the initial site/source of injury/irritation is still active on some level and capable of maintaining or restarting the initial CRPS.

Harbut and Correll recently reported the successful treatment of a 9-year case of Type I CRPS with intravenous ketamine-infusion therapy in a warfarin-anticoagulated adult female patient [1,28]. Ketamine was administered as an inpatient subanesthetic (i.e., low-dose) infusion with a gradual titration of relief against side effects while maintaining full patient awareness (i.e., the patient was awake). This treatment approach provided

sufficient drug exposure over time to achieve the desired objective of desensitization. The patient obtained complete relief of her lower extremity CRPS. The patient remained pain free for 18 months. Thereafter, some pain symptoms returned, but they corresponded with the recurrence of a femoral artery clot.

There have also been reports of another type of ketamine-based desensitization therapy using a high-dose (5–7 mg/kg/hr) ketamine infusion technique for 5–7 days duration [29,30]. However, this different higher-dose approach requires that the CRPS patient be admitted to an intensive care unit, as he or she will more likely be rendered unconscious.

Clearly, better treatment methodologies are needed for patients who continue to suffer with CRPS that will not respond to conventional therapies. The purpose of this paper is to retrospectively analyze data collected in Mackay, Australia, that we believe further illustrate the efficacy of the particular inpatient low-dose ketamine infusion technique previously described by the authors [1,31].

Methods

This retrospective study examined patients with Type I and Type II CRPS who received low-dose inpatient ketamine infusion treatments between 1996 and 2002 in Mackay, Australia. All the patients treated were initially diagnosed by the orthopedics department and referred for pain management. The senior anesthesiologist administering the low-dose ketamine treatment also confirmed the diagnosis of CRPS. The diagnostic criteria used included the presence of sensorimotor and autonomic disturbances in the affected area.

Patient records were reviewed and the data that was obtained was analyzed for demographic parameters, pain intensity, pain duration, and site of CRPS that prompted the treatment with ketamine infusion. All patients treated with low-dose ketamine infusions had agreed to receive this alternate therapy after being informed and giving consent. Most patients had failed to achieve pain relief through conventional treatment.

Generally, the ketamine infusions were started at a rate of 10 mg/hr. The rate was increased in small increments, as tolerated, until the onset of what patients typically describe as a feeling of inebriation or its equivalent. The onset of this particular CNS symptom appeared to be necessary to help guide us in reaching what we believe is, or is close to, the minimally effective infusion rate for ketamine. Once the effective rate was achieved, it was continued as long as the patient tolerated the drug and continued benefit was observed. If unacceptable side effects were noted, the rate was decreased or the infusion was temporarily discontinued. The highest tolerated dose producing analgesia (i.e., without unacceptable side effects) was continued for the duration of the infusion.

Except with Patient 14 and Patient 19, all ketamine treatment cycles were generally discontinued as follows: A) After 12–24 hours of complete CRPS pain relief; B) 24 hours after an initial partial response that would not improve any further; or C) After 48 hours of a continuous lack of improvement in the pain score. In two patients, the infusion therapy was administered for less than 1 day (Tables 1–3).

Recording of pain scores and duration of pain relief, if present, were used to assess the efficacy of this treatment method. After recording the pre- and postinfusion verbal numeric pain scores of 0–10, in which 0 indicates no pain and 10 corresponds to the worst pain imaginable, the percentage of pain relief following the treatment was calculated as follows:

$$\%\ \text{Pain Relief} = \frac{\text{BPS} - \text{PKPS}}{\text{BPS}} \times 100$$

where BPS is baseline pain score and PKPS is postketamine pain score.

It is clear that improvement in CRPS involves the reduction and remission of multiple accompanying symptoms. Due to the retrospective nature of this analysis and the fact that pain is the most disabling feature of this condition, the assessment of other symptomatic responses was not the primary focus in this study.

For simplicity of analysis, only data indicating the percent pain relief and the duration of this relief were considered as outcome measures. The duration of pain relief was analyzed by Kaplan-Meier survival analysis. In this analysis, patients who relapsed were considered to have reached an end point. The two patients who did not experience pain relief were treated as immediate relapses. Patients with immediate relief but no follow-up were counted as initial successes, but "censored" at time zero. The standard error is provided for selected curve points to indicate the precision of the estimate. Due to repeated infusion in a subgroup of patients, a second analysis was performed after the second treatment. Since a third treatment

Table 1 Patient demographics, CRPS history, ketamine therapy, and outcome data

Demographics			CRPS History		Ketamine Infusion		Outcome†		
No.	Age	Sex	Duration (months)	Involved Region	Dosage* (mg/hr)	Duration (days)	% Pain Relief	Duration (months)	Comments and Complications
1	48	M	3	Foot	15–20	0.75	100	>1.25	Failed to follow up
2	22	M	0.25	Sciatic nerve	10–20	0.75	100	>5	Sciatic nerve injury with acute CRPS II
3	46	F	60	Wrist	10–15	1	70	>2	CRPS developed following tendon repair
4	68	M	8	Leg	15–30	11	85	No follow-up	Failed to follow up
5	42	M	5	Hand	20	3	100	4	Posttraumatic CRPS
6	25	M	1	Ankle	10–20	2	100	9	Posttraumatic CRPS
7	52	M	4	Foot	16–18	3	100	>2	CRPS with ulcers, which healed postinfusion
8	40	M	42	Foot	10–15	5	100	>24	Posttraumatic CRPS
9	33	M	6	Hand	15–50	20	100	3	Elevated LFTs resulted in early termination of second infusion
10	55	F	7	Wrist	15	3	100	>0.75	Posttraumatic CRPS with no response to guanethidine blocks
11	36	M	1.25	Ankle	20–26	3.5	100	No follow-up	Posttraumatic CRPS; failed to follow up
12	15	M	0.3	Leg and ankle	10–15	3	70	>2	Posttraumatic CRPS; patient was completely pain free upon last follow-up
13	36	M	>24	Foot and ankle	12.5–46	5	40	No follow-up	40% relief of spontaneous pain; no relief of evoked pain; post fasciotomy
14	20	F	36	Ankle	50	14	0	N/A	Patient on >1 g/day morphine
15	60	F	3	Hand	15–20	4	100	>24	CRPS due to animal bite injury
16	15	M	0.3	Ankle	15–18	4	100	No follow-up	Traumatic acute CRPS; failed to follow up
17	40	M	6	Foot	15	4	100	No follow-up	Posttraumatic CRPS; failed to follow up
18	21	M	0.3	Ankle	18	4	100	36	Fracture-related acute CRPS
19	27	F	60	Hand	50	5	0	N/A	Posttraumatic CRPS; on high-dose morphine
20	58	F	6	Knee	15	4	100	>6	Arthroscopic surgery after infusion
21	46	M	84	Arm	20	14	100	3	Elevated LFTs resulted in early termination of two more infusions
22	44	M	60	Hip & thigh	a) 15–20 b) 15–20	1.58 5	75 100	2 12	Pain relief correlated with duration of infusion (a vs b)
23	40	M	96	Ankle	a) 20–30 b) 20–30	10 2	100 100	2.5 >15	Posttraumatic CRPS requiring seven corrective surgeries and amputation, with persisting pain
24	47	F	6	Hand	a) 30 b) 22	12 2	100 100	4 >3	Posttraumatic CRPS
25	45	M	240	Foot	a) 10–15 b) 10–40	5 7	100 100	6 >6	Patient had mild elevated LFTs and a diabetic polyneuropathy.
26	60	M	1.5	Thumb	a) 15 b) 15	4 6	100 100	3 >36	CRPS developed after a joint fusion for severe arthritis
27	52	M	36	Hand	a) 20–25 b) 15–30	1 2	100 100	0.75 No follow-up	Type II CRPS secondary to ulnar nerve neuropathy; failed to follow up
28	30	M	60	Foot	a) 20–25 b) 25	5 4	100 100	4 >12	Posttraumatic CRPS

Table 1 Continued

Demographics			CRPS History		Ketamine Infusion		Outcome†		
No.	Age	Sex	Duration (months)	Involved Region	Dosage* (mg/hr)	Duration (days)	% Pain Relief	Duration (months)	Comments and Complications
29	31	F	4	Arm & Shoulder	a) 15 b) 15	3 7	100 100	4 >3	Patient received a second treatment due to relapse after returning to work
30	47	M	24	Ankle	a) 20–25 b) 20–25	4 3	85 100	1 4	Posttraumatic CRPS; due to elevated LFTs treatment was terminated early
31	44	M	6	Heel	a) 15 b) 17.5	4 4	100 100	1 No follow-up	Post-traumatic CRPS Failed to follow up
32	32	M	36	Bilateral hands	a) 15–20 b) 15–20 c) 15–20	3 3 3	100 100 100	7 36 >6	CRPS due to repeated microtrauma to both hands by long-term use of jackhammer
33	59	M	0.25	Bilateral shoulders	a) 10–20 b) 10–25 c) 10–25	2 2 3	100 100 100	2 12 >36	CRPS developed after shoulder surgery first on the left (a & b) and 14 months later on the right side (c)

* Presented are the mean and/or maximum dosages of ketamine infusion.
† Outcome data refer to immediate pain relief after the infusion followed by the duration of the pain relief. The numerical value that follows the > symbol refers to the duration of relief at the last visit upon which the patient was still pain free. The labels a, b, and c indicate the first, second, and third cycles of ketamine infusion therapy in a given patient, respectively.

Table 2 Analysis of data from Table 1

	Patient Age (years)	Duration CRPS (months)	Ketamine (maximum) Infusion Rate (mg/hr)	Duration of Infusion (days)	Immediate Response (% relief)
Mean	40.5	28.1	23.4	4.7	92
Median	42	6	20	4.0	100
Standard deviation	13.8	47	9.6	3.86	22.25
Interquartile range (25th–75th percentiles)	30.5–50	2.25–39	15–25	3–5	83% got 100% relief initially
Maximum/minimum	68/15	240/0.25	50/15	20/0.75	100/0

Note: Except for age, all calculated values were obtained by combining data from all 47 treatment cycles (this includes patients who had repeat treatments). The mean and median ages were based on 33 patients.

cycle was present in only two patients, a third subgroup analysis was not performed.

Kaplan-Meier curves are commonly used for survival analysis. They were used here to illustrate the time course over which the maintenance of relief was gradually lost. This methodology was particularly helpful in this study as patients had different follow-up times and not all individuals reached a definite end point under observation (i.e., failure of relief or relapse). It should be noted that these curves are based on relatively small sample sizes and are thus subject to considerable random error.

Table 3 Maximum dose of ketamine infusion

Ketamine Infusion Rate (max) (mg/hr)	During the first Infusion (N = 33)	During the second Infusion (N = 12)	All treatments combined (N = 47)*
≤15	10 (30%)	2 (17%)	12 (26%)
16–20	12 (36%)	3 (25%)	16 (34%)
21–25	3 (9%)	4 (33%)	8 (17%)
26–30	4 (12%)	2 (17%)	6 (13%)
>30	4 (12%)	1 (8%)	5 (11%)

Note: Percentage distribution of infused maximum ketamine dose within the combined 47 treatment cycles compared with the dosing used in the first and second treatment cycles.
* Includes a third cycle of treatment in two additional patients.

All the individual patient data obtained are presented in Table 1. Different variables were analyzed in terms of their recurrence rates and temporal distributions. Follow-up visits and failures to follow-up were recorded. The purpose of this retrospective review was to determine if the inpatient use of low-dose infusions of ketamine provided any degree of meaningful improvement

Table 4 Duration of Infusion Therapy

Duration of treatment cycle (days)	Number of patients receiving 1 treatment cycle (N = 33)	Number of patients receiving 2 treatment cycles (N = 12)	Number of patients receiving 3 treatment cycles (N = 2)	All infusions combined (N = 47)
<2	5 (15%)	0	0	5 (11%)
2–3	8 (24%)	6 (50%)	2 (100%)	16 (34%)
4–5*	14 (42%)	3 (25%)	0	17 (36%)
6–7	0	3 (25%)	0	3 (6%)
≥8	6 (18%)	0	0	6 (13%)

A total of 33 patients received ketamine infusion therapy. Some patients at later times received a second and even third cycle of treatment. The data here organize each treatment cycle into 1 of 5 duration categories.
* One treatment cycle lasting 3.5 days was included in this category (see Table 1, Patient 11).

in pain scores, and thus, quality of life, in patients suffering from CRPS. To achieve that objective we focused our analysis on the relief obtained by patients undergoing this novel treatment option.

Results

Thirty-five patient charts with a diagnosis of CRPS were reviewed for the current retrospective analysis. Thirty-three patients are included in the current assessment and analysis. Two patients were excluded due to insufficient data. The study group consisted of 25 men and eight women, with a male-to-female ratio of approximately 3:1. The average age of all individuals was 40.5 years (40 for men and 43 for women); more than 75% of all patients were younger than 48 years of age (Tables 1 and 2).

Except for two individuals, the remaining 31 of 33 patients were suffering from Type I CRPS (reflex sympathetic dystrophy). Patient 2 and Patient 27 were later diagnosed with an acute traumatic sciatic nerve injury and ulnar nerve neuropathy, respectively, and had Type II CRPS (causalgia). Patient 25 was diagnosed with a diabetes-related peripheral polyneuropathy; however, Type I CRPS was affecting his distal right lower extremity and it appeared to have preceded the onset of his diabetic polyneuropathy.

The median duration of CRPS pain was 6 months; 39% (13) of patients had CRPS for more than 2 years. In one individual, the condition was ongoing for more than 20 years; hence, the relatively skewed average value of CRPS duration (28 months). In 15% of cases (five individuals), the condition was present for ≤3 weeks (Table 1; Discussion).

In three patients, the CRPS was affecting primarily the proximal limb (two patients with shoulder/arm and one patient with thigh/hip region involvement). In all other patients, the condition involved a distal extremity.

The low-dose intravenous ketamine infusion therapy was administered to 21 (64%) of 33 patients only once (Table 1, Patients 1–21). Ten (30%) of 33 patients (Patients 22–31) received a second treatment, and two (6%) of 33 patients (Patients 32–33) received second and third courses of treatment. The total number of administered infusion cycles for all 33 patients was 47 treatments.

In 17 of 47 total infusion cycles (36%), the infusion rate was maintained at the upper tolerated titration level. However, during the other 30 of 47 infusion cycles (64%), the tolerated dosage required ongoing adjustment (Table 1). The average maximum infusion rate was 23.4 mg/hr. During 78% of all infusion cycles, patients received ketamine at a rate ≤25 mg/hr. Comparing the percentage distribution of the maximum ketamine dosing, patients given a second infusion cycle received a slightly higher infusion rate of ketamine than during the first round of therapy, that is, a slight shift of the maximum from 15–20 to 20–25 mg/hr (Table 3; Discussion). Due to insufficient responses in Patients 9, 13, and 25, the maximum infusion rates were increased to 50, 46, and 40 mg/hr, respectively. This increase was done in an attempt to maximize any potential benefit for the patients. In two other patients (Patients 14 and 19), there was no response to therapy despite ketamine titration up to 50 mg/hr (see below; Tables 1–3).

The duration of infusion therapy was from 2–5 days in 70% of all treatment cycles (Table 4). In 5 cycles (11%), the treatment was performed for <2 days, and in 6 others (13%), it was continued for ≥8 days. Patient 9 had an exceptionally long treatment interval, lasting up to 20 days (Table 2). This exceptionally long treatment trial resulted in only 3 months of relief. Subsequently, a repeat

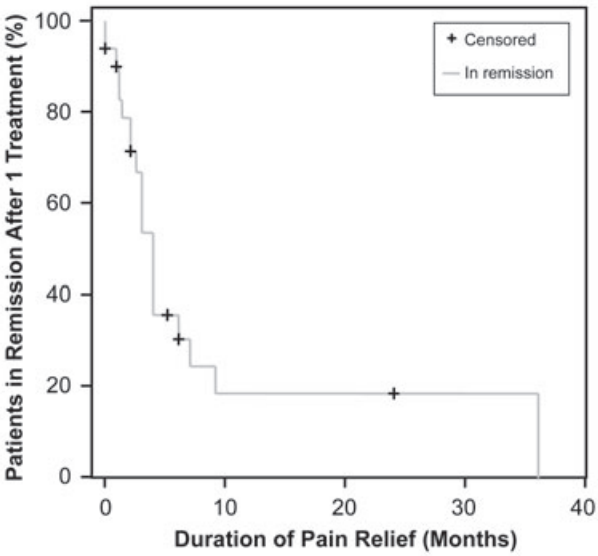

Figure 1 Cumulative treatment outcome for duration of pain relief after 33 patients received their first ketamine infusion. Each + sign refers to one or more censored patients. A censored patient is one who was still in remission (partial or complete) as of his or her last clinic visit; the + sign indicates the time each censored patient was last evaluated. The actual number of censored patients at each indicated time was as follows: five at 0 months; one at 0.75 months; three at 2 months; one at 5 months; one at 6 months; and two at 24 months (13 total).

treatment resulted in elevated liver function tests (LFTs) that required premature termination of the treatment.

The immediate response to therapy, that is, pain relief, was complete (100% relief) in 25 of 33 patients (76%), whereas six others (18%) had only partial relief, and the remaining two patients (6%) had no response. In contrast to the first cycle of treatment, all repeat treatments achieved 100% immediate pain relief. Considering the immediate response of all 47 treatment cycles administered (i.e., combined initial and all repeat treatments), the responses to therapy resulted in 39 with complete relief (83%), six with partial relief (13%), and two without relief (4%) (Tables 1 and 2).

Both nonresponders (Patients 14 and 19) were maintained on high doses of oral morphine prior to and during the ketamine-infusion therapy. They were treated with the highest doses of ketamine (50 mg/hr) used. They failed to respond despite treatment durations of 14 days with Patient 14 and 5 days with Patient 19 (Table 1).

The duration of pain relief after the first ketamine infusion was analyzed according to the Kaplan-Meier survival function. This analysis indicated that an average of 54% of the patients experienced ≥3 months of pain relief and that, in 31% of the individuals, the relief lasted ≥6 months (Figure 1; Table 5). In patients who underwent a second course of ketamine infusion, the results indicate that 58% of the patients had relief for at least 1 year and that almost a third of the patients remained pain free beyond 3 years (Figure 2; Table 5).

In terms of side effects, four individuals (Patients 9, 21, 25, and 30) developed elevated hepatic enzyme profiles that resolved following discontinuation of the ketamine infusion. Due to an ongoing but very slow response, Patient 21 was one of the exceptional cases who required 14 days of continued ketamine infusion. Despite a relatively low dose of 20 mg/hr (which eventually completely eliminated his pain), he developed elevated liver enzyme levels toward the end of his treatment. After 3 months, he suffered a relapse of his pain. Unfortunately, two more attempted trials of ketamine infusion resulted in immediate elevation of his liver-enzyme profile, thus requiring that treatment be abandoned within the first 48 hours (not plotted in Table 1).

CNS side effects, such as a feeling of inebriation, dizziness, and (to a lesser extent) blurred vision and nausea, were relatively common. Their onset was a sign used in gauging therapy and establishing the initially tolerated upper-infusion rate. If one considers the initial upper level of ket-

Table 5 Analysis of treatment outcomes

Analysis of Treatment Outcomes		Duration of Relief (months)	Standard Error	95% Confidence Interval
After the first infusion:	Mean	9.44	2.93	3.70–15.17
(N = 33; 13 censored; 20 events)	Median	4.00	0.48	3.07–4.93
After the second Infusion:	Mean	25.00	5.68	13.86–36.14
(N = 12; 8 censored; 4 events)	Median	36.00	18.61	0.00–72.47

The mean and median durations of relief were assessed after the first and second infusions. A censored patient is one who was still in remission (partial or complete) as of his or her last clinic visit. An event is a relapse or failure of treatment.

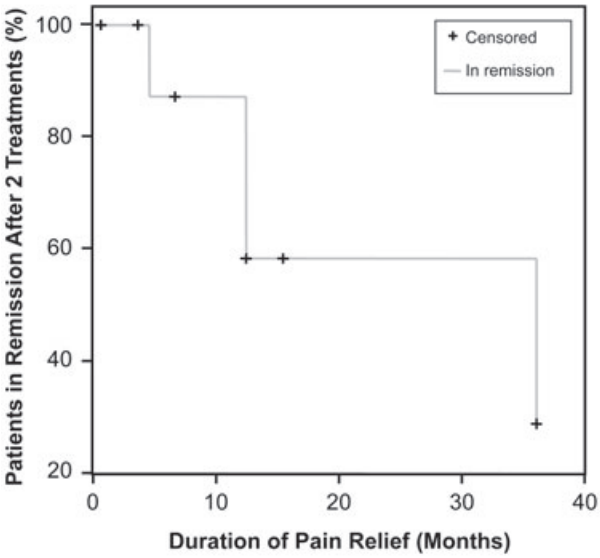

Figure 2 Cumulative treatment outcome for duration of pain relief after 12 patients received their second ketamine infusion. Each + sign refers to one or more censored patients. A censored patient is one who was still in remission (partial or complete) as of his or her last clinic visit; the + sign indicates the time each censored patient was last evaluated. The actual number of censored patients at each indicated time was as follows: two at 0 months; two at 3 months; one at 6 months; one at 12 months; one at 15 months; and one at 36 months (8 total).

amine infusion rate tolerated as an initial benchmark, then in 17 of 47 cumulative infusion cycles (36%) that infusion rate remained constant, while in 30 of 47 cycles (64%), the tolerated dosage required ongoing adjustment. During only 9 of 47 combined infusion therapies (19%) was the ketamine dose increased above 26 mg/hr. Except for Patient 24, who received 12 days of ketamine infusion at 30 mg/hr, and the two nonresponders, with ongoing infusion rates of 50 mg/hr, all individuals receiving dosing greater than 26 mg/hr required ongoing adjustment of their infusion.

Inebriation, in particular, was very frequent during the first 24 hours of therapy, and its onset was used as an end point of titration (i.e., no further increases in infusion rate). Hallucinations occurred in six patients. No-one experienced sedation. There were no suicidal and/or homicidal tendencies. We also did not observe any ketamine-related addictive behaviors.

Discussion

The severity of CRPS pain, as well as its chronic nature and resistance to currently available treatment modalities, has a devastating impact on patients and their relationships with others. In addition to pain, affected individuals also suffer from a lack of appropriate use of their involved limb(s); this can result in major frustration, depression, anger, isolation, and loss of job, with major psychosocial and socioeconomic consequences. CRPS challenges patients, their loved ones, and health care providers with unyielding defiance.

Although ketamine may have more than one mechanism of action, the basis for using it to treat CRPS may reside in its strong ability to block NMDA receptors. Experimental evidence suggests that a sufficiently intense or prolonged painful stimulus causes an extraordinary release of glutamate from peripheral nociceptive afferents onto dorsal horn neurons within the spinal cord. The glutamate released, in turn, stimulates NMDA receptors on second-order neurons that produce the phenomena of windup and central sensitization. It is reasonable to consider that, by blocking NMDA receptors, one might also be able to block cellular mechanisms supporting windup and central sensitization [4–7,15]. Ketamine is the only potent NMDA-blocking drug currently available for clinical use. Our interpretation is that an appropriately prolonged infusion of ketamine appears to maintain a level of ketamine in the central nervous system long enough to reverse the effects of the sensitization process and associated pain.

In this retrospective analysis, adult individuals made up the majority of the patients. Seventy-six percent of all patients were younger than 48 years of age (Tables 1 and 2). The age distribution of the patients was similar to other reports in the literature [32]; the number of male patients was disproportionately high in this study. The male-to-female ratio of 3:1 is actually the reverse of what is seen in the majority of CRPS studies. This may be related to the referral base of a regional hospital, compared with a tertiary care university center, from where most of the studies originate.

In 30 patients (91%), the CRPS was affecting a distal extremity. The remaining three individuals had distal sensory and autonomic abnormalities despite the fact that the site of CRPS onset and maximum pain was in the proximal part of the involved extremity. In five patients the condition was fairly acute and of less than 1 month in duration. Nevertheless, it did appear to the physicians evaluating these patients that they indeed had early CRPS, as opposed to acute posttraumatic nociceptive pain. The patients were offered this

alternative treatment and they recovered. We recognize that, in those five, patients the CRPS symptoms might have improved spontaneously.

It is impressive to note that the treatment has the potential of eliminating even the pain of those patients who have been suffering from the condition for several years, and not just more recently developed cases. In the case of Patient 25, CRPS was present for more than 20 years until it was completely suppressed with the ketamine infusion. This also points out the dynamic nature of the pain processing system and its long-lasting responsiveness to what appears to be neuromodulation therapy.

There were potential issues complicating interpretation of the outcome data. Due to the retrospective nature of this analysis and the fact that pain is the most disabling feature of CRPS, assessment of other symptomatic responses to ketamine infusion were not included in this study. The analysis only studied the percentage of pain relief and the duration of the relief.

Kaplan-Meier survival analysis was used to determine the duration of pain relief. The analysis performed for the first course of ketamine infusion indicated that about 54% of the patients experienced 3 months of pain relief and 31% of the patients experienced 6 months or more of pain relief. In patients undergoing a second course of ketamine infusion, the results indicate at least a 1-year period of pain relief in 58% of individuals. After the second treatment, almost a third of the patients remained pain free beyond the 3-year follow up (Figures 1 and 2; Table 5). Since it is likely that patients who relapsed are more motivated to remain in the system and return for follow up than patients who remained pain free, the above Kaplan-Meier estimates are probably conservative.

The reasons why the second infusion resulted in a more profound relief of pain with a longer pain-free interval may be different for each patient. One major factor may be the presence of lower pain intensity at the beginning of the second therapy versus the first. Indeed, many of the individuals undergoing the second treatment had, on average, a lower pain rating than during their first therapy (not depicted in the result section); that is, the relapse of pain was not complete, and they underwent a second course of therapy while still having a partial response. Comparing the percent distribution of the maximum ketamine dosing, during the second infusion cycle patients received a slightly higher infusion rate of ketamine than during the first round of therapy, that is, a slight shift of the maximum from 15–20 to 20–25 mg/hr. This difference is only present when the cumulative data of all patients receiving the first infusion are compared with those of the patients receiving the second treatment. However, performing a paired analysis of the data in the same individuals undergoing a repeat treatment did not support this difference. Whether psychological factors such as previous experience or better adaptation to side effects resulted in tolerating a slightly higher dosing during the second course of therapy requires further studies; nevertheless, this increase in the hourly administered maximum ketamine dosing might have contributed to the higher response rate and longer duration of remission after the second treatment as well.

The two patients who failed to respond (Patients 14 and 19) were using high-dose opiates; and also, both previously failed sympathetic blocks. Both patients were given very high doses of ketamine infusion therapy (50 mg/hr) and, despite the relatively long duration of the treatment (14 and 5 days, respectively), both failed to show any readily apparent response to ketamine. Patient 14 was ultimately lost to follow-up as she left the region. Patient 19's narcotic was switched to methadone but with no improvement. She was eventually weaned off all narcotics, although her pain continued.

Morphine tolerance has been shown to decrease the analgesic effects of ketamine in animal models [33], and the activation of NMDA receptors has been demonstrated to attenuate acute responsiveness of δ-opioid receptors, indicating a major crosstalk between NMDA and opioid signal transduction [34]. Concurrent use of opiates can complicate treatment by signs of withdrawal if they are tapered during treatment, thus making the careful adjustment of the ketamine dosing problematic. There is also evidence from animal experiments supporting the activation of NMDA receptors and induction of allodynia and myoclonus by morphine-3-glucuronide (M3G), an active metabolite of morphine [35–40]. The possibility must be considered that morphine may contribute to the allodynia and complicate the treatment of these patients.

Most patients receiving more than 35 mg/hr maximum ketamine infusion doses were noted to be either nonresponders or to have experienced side effects resulting in interruption of treatment (see below). If tolerated, the infusion of ketamine was titrated up and continued at the maximum dose of 30 mg/hr during the first day.

CNS side effects, such as a feeling of inebriation, dizziness, and (to a lesser extent) blurred vision and nausea, were relatively common. Inebriation, in particular, was very frequent during the first 24 hours of therapy. No sedation was noted, and there was no need for intubation. Hallucinations occurred in six patients. There were no observed ketamine-related addictive behaviors.

During the titration process, the onset of a tolerable feeling of inebriation (or equivalent) was an important indicator in determining each patient's target therapeutic infusion rate. Although some rate adjustments may be beneficial (over the treatment period), greatly exceeding or diminishing this target rate may not be required or wanted and may be increasingly likely to bring with it unwanted CNS side effects or diminished effectiveness. Therefore, we hypothesize that the onset of a feeling of inebriation or equivalent essentially indicates when a therapeutic level of ketamine within the CNS has been reached. If the infusion rate is thereafter maintained over time (and/or moderately adjusted as tolerated), we hypothesize that this "therapeutic level" will be sufficient enough to induce a desensitization response resulting in pain relief in patients who respond to this treatment option.

In four individuals (Patients 9, 21, 25, and 30; Table 1), treatment resulted in elevations of liver enzymes, which improved following discontinuation of therapy. Patients 9 and 21 had exceptionally long durations of infusion, lasting for 20 and 14 days, respectively. To what extent they might have had preexisting pathology predisposing them to enzyme elevation was not clear. Nevertheless, these individuals who initially developed enzyme abnormalities redeveloped them with subsequent infusions. It is also unknown whether or not individuals with this type of susceptibility to ketamine remain at a higher risk for developing other types of hepatic dysfunction. Therefore, prior to and during the treatment, patients need to be carefully assessed and monitored for the presence or development of any hepatic pathology.

Due to the focus of this retrospective review and the limitations of the data recorded, we were only able to evaluate the degree and duration of pain relief obtained. We could not and did not evaluate any other effects or side effects related to the use of ketamine other than those described.

The long-term effect of ketamine therapy as it might relate to neurotoxicity in humans is not currently known. The maximal rates of ketamine infusion described in this review ranged from 25–50 mg/hr. Others have explored the use of much higher infusion rates of ketamine (5–7 mg/kg/hr for durations up to 7 days) in patients with intractable CRPS with no reported long-term neurotoxic effects [29,30]. Nevertheless, based on animal studies, a concern for potential neurotoxic effects caused by NMDA-receptor antagonists has been raised (Appendix 1) [41–58]. In light of these raised concerns, the occasional use of longer durations of low-dose ketamine therapy, described herein, is not now something we recommend. What relationship the neurotoxic effects seen in animals (after a high dose of ketamine) have in terms of any potential similar effect in humans (after a prolonged low-dose infusion of ketamine) is not known. Thus, for now, it seems prudent that practitioners weigh any interest in using this inpatient treatment against the potential for any possible long-term effects of this therapy in humans. Likewise, for now, it may also be prudent to avoid using higher dose infusions as well as longer duration treatments.

As with any new treatment, the potential for known or unknown side effects should be discussed with and acknowledged by each prospective patient. In the years ahead, the effect of prolonged infusions of both low- and high-dose ketamine infusion therapy on the potential for causing neurotoxicity, and/or any other side effects, will need to be investigated further. However, until that time, we propose to limit the duration of a continuous ketamine infusion treatment to a maximum of 4–5 days and, furthermore, to limit the maximum infusion rate to about 25–50 mg/hr. Such a proposal is offered here not to restrict future treatments and study, but to promote caution in the further exploration of the efficacy and safety of this new treatment option that is as yet still in early development. Furthermore, with safety in mind, it may also be prudent to incorporate the coadministration of a neuroprotective agent to minimize the potential for the development of the neurotoxic effects that have been observed in animals (Appendix 1).

In conclusion, this retrospective review provides some additional evidence that the use of a low-dose infusion of ketamine may be a useful option in the treatment of patients with intolerable CRPS. We do not propose that this treatment will be useful in all CRPS patients; however, we do believe that a limited and individualized inpatient infusion trial may provide an effective and relatively safe treatment option for appropriately selected patients who do not respond, or are not expected to respond, to conventional treatment

modalities. The patient safety issues of greatest concern appear to be the potential for hepatic dysfunction and CNS side effects. With regard to future treatment strategies, we recommend a careful review of Appendix 1 regarding the coadministration of a neuroprotective agent.

References

1 Harbut RE, Correll GE. Successful treatment of a nine-year case of complex regional pain syndrome type-I (reflex sympathetic dystrophy) with intravenous ketamine-infusion therapy in a warfarin-anticoagulated adult female patient. Pain Med 2002;3:147–55.

2 Mendell LM. Physiological properties of unmyelinated fiber projection to the spinal cord. Pain 1966;41:309–21.

3 Pockett S. Spinal cord synaptic plasticity and chronic pain. Anesth Analg 1995;80:173–9.

4 Mannion RJ, Woolf CJ. Pain Mechanisms and Management: A Central Perspective. Clin J Pain 2000;16(3 suppl):S144–56.

5 Carpenter KJ, Dickenson AH. NMDA receptors and pain—hopes for novel analgesics. Reg Anesth Pain Med 1999;24:506–8.

6 Ahmad M, Ackerman WE, Munir MA, Saleem M. NMDA receptor antagonists. Recent advances in chronic pain. Pain Clinic 2001;April:25–31.

7 Bennett GJ. Update on the neurophysiology of pain transmission and modulation: Focus on the NMDA-receptor. J Pain Symptom Manage 2000;19(1 suppl):S2–6.

8 Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: Implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293–9.

9 Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management: Preclinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage 2000;20:358–73.

10 Sher MH. Slow dose ketamine—a new technique. Anaesth Intensive Care 1980;8:359–61.

11 Pandit SK, Kothary SP, Kumar SM. Low dose intravenous infusion technique with ketamine. Amnesic, analgesic and sedative effects in human volunteers. Anaesthesia 1980;35:669–75.

12 Ito Y, Ichiyanagi K. Post-operative pain relief with ketamine infusion. Anaesthesia 1974;29:222–6.

13 Clausen L, Sinclair DM, Van Hasselt CH. Intravenous ketamine for postoperative analgesia. S Afr Med J 1975;49:1437–40.

14 Sang CN. NMDA-receptor antagonists in neuropathic pain: Experimental methods to clinical trials. J Pain Symptom Manage 2000;19(1 suppl):S21–5.

15 Backonja M, Arndt G, Gombar KA, Check B, Zimmermann M. Response of chronic neuropathic pain syndromes to ketamine: A preliminary study. Pain 1994;56:51–7.

16 Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: A double-blind, cross-over comparison with morphine and placebo. Pain 1994;58:347–54.

17 Klepstad P, Borchgrevink PC. Four years' treatment with ketamine and a trial of dextromethorphan in a patient with severe post-herpetic neuralgia. Acta Anaesthesiol Scand 1997;41:422–6.

18 Hoffmann V, Coppejans H, Vercauteren M, Adriaensen H. Successful treatment of postherpetic neuralgia with oral ketamine. Clin J Pain 1994;10: 240–2.

19 Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurology 1997;48:1212–8.

20 Sang CN, Parada S, Booher S, et al. A double blinded randomized controlled trial of dextromethorphan versus memantine versus placebo in subjects with painful diabetic neuropathy and postherpetic neuralgia. Presented at the 16th Annual scientific meeting of the American Pain Society. San Diego, CA, November, 1997.

21 Kinoshita Y, Takakura K, Yanagimoto M, Fujibayashi T, Sugiura Y, Goto Y. Evaluation of ketamine infusion treatment for patients with chronic pain. Hokuriku J Anesthesiol 1997;31:11–14.

22 Tsuneyoshi I, Gushiken T, Kanmura Y, Yoshimura N. Changes in pain intensity of post-herpetic neuralgia following intravenous injections of ketamine hydrochloride. J Anesth 1999;13:53–5.

23 Wong CS, Shen TT, Liaw WJ, Cherng CH, Ho ST. Epidural coadministration of ketamine, morphine and bupivacaine attenuates post-herpetic neuralgia—a case report. Acta Anaesthesiol Sin 1996;34:151–5.

24 Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: A central neuropathic disorder maintained by peripheral input. Pain 1996;67:69–77.

25 Nikolajsen L, Hansen PO, Jensen TS. Oral ketamine therapy in the treatment of postamputation stump pain. Acta Anaesthesiol Scand 1997;41:427–9.

26 Mitchell AC. An unusual case of chronic neuropathic pain responds to an optimum frequency of intravenous ketamine infusions. J Pain Symptom Manage 2001;21:443–6.

27 Bennett GJ, Maleki J. The multiplicity of neuropathic pain sensations. Pain Forum 1998;7:243–5.

28 Maleki J. "Sensitization": Is there a cure? Pain Med 2002;3:294–7.

29 Kiefer RT, Rohr P, Unertl K, Altemeyer KH, Grothusen J, Schwartzman RJ. Recovery from intractable complex regional pain syndrome type-I (RSD) under high dose intravenous ketamine-

midazolam sedation. Neurology 2002;58(suppl 3): A-474.
30 Kiefer RT, Rohr P, Ploppa A, Unertl K, Schwartzman RJ. Is high dosed ketamine a therapeutic option for severe intractable Complex Regional Pain Syndrome? Anesthesiology 2003;99:A1008.
31 Correll GE, Muir JJ, Harbut RE. Use of ketamine infusion in patients with complex regional pain syndrome. J Pain 2002;3(suppl):S17.
32 Low PA, Wilson PR, Sandroni P, Willner CL, Chelimsky TC. Clinical characteristics of patients with reflex sympathetic dystrophy. In: Jaenig W, Stanton-Hicks M, editors. Reflex sympathetic dystrophy: A reappraisal. Seattle: IASP Press;1996:49–66.
33 Finck AD, Samaniego E, Ngai SH. Morphine tolerance decreases the analgesic effects of ketamine in mice. Anesthesiology 1988;68:397–400.
34 Cai YC, Ma L, Fan GH, Zhao J, Jiang LZ, Pei G. Activation of N-methyl-D-aspartate receptor attenuates acute responsiveness of delta-opioid receptors. Mol Pharmacol 1997;51:583–7.
35 Smith MT. Neuroexcitatory effects of morphine and hydromorphone: Evidence implicating the 3-glucuronide metabolites. Clin Exp Pharmacol Physiol 2000;27:524–8.
36 Bartlett SE, Cramond T, Smith MT. The excitatory effects of morphine-3-glucuronide are attenuated by LY274614, a competitive NMDA receptor antagonist, and by midazolam, an agonist at the benzodiazepine site on the GABAA receptor complex. Life Sci 1994;54:687–94.
37 Labella FS, Pinsky C, Havlicek V. Morphine derivatives with diminished opiate receptor potency show enhanced central excitatory activity. Brain Res 1979;174:263–71.
38 Wright AW, Mather LE, Smith MT. Hydromorphone-3-glucuronide: A more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. Life Sci 2001;69:409–20.
39 Moran TD, Smith PA. Morphine-3beta-D-glucuronide suppresses inhibitory synaptic transmission in rat substantia gelatinosa. J Pharmacol Exp Ther 2002;302:568–76.
40 Hemstapat K, Monteith GR, Smith D, Smith MT. Morphine-3-glucuronide's neuro-excitatory effects are mediated via indirect activation of N-methyl-D-aspartic acid receptors: Mechanistic studies in embryonic cultured hippocampal neurones. Anesth Analg 2003;97:494–505.
41 Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 1989;244: 1360–2.
42 Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, and Sesma MA. NMDA antagonist neurotoxicity: Mechanism and prevention. Science 1991;254:1515–8.
43 Jevtovic-Todorovic V, Wozniak DF, Benshoff ND, Olney JW. A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. Brain Res 2001;895:264–7.
44 Ellison G. Competitive and non-competitive NMDA antagonists induce similar limbic degeneration. Neuroreport 1994;5:2688–92.
45 Fix AS, Long GG, Wozniak DF, Olney JW. Pathomorphologic effects of N-methyl-D-aspartate antagonists in the rat posterior cingulate/retrosplenial cerebral cortex: A review. Drug Dev Res 1994;24: 147–52.
46 Corso TD, Sesma MA, Tenkova TI, Der TC, Wozniak DF, Farber NB, Olney JW. Multifocal brain damage induced by phencyclidine is augmented by pilocarpine. Brain Res 1997;752:1–14.
47 Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994;51:199–214.
48 Malhotra AK, Pinals DA, Adler CM, Elman I, Clifton A, Pickar D, Breier A. Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology 1997;17:141–50.
49 Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, Olney JW. Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology 1999;20:106–18.
50 Jevtovic-Todorovic V, Olney JW. Neuroprotective agents. In: Evers AS, Mayes M, editors. Anesthetic pharmacology, physiologic principles and clinical practice. Philadelphia: Churchill Livingstone; 2004:557–72.
51 Farber NB, Foster J, Duhan NL, Olney JW. Alpha 2 adrenergic agonists prevent MK-801 neurotoxicity. Neuropsychopharmacology 1995;12:347–9.
52 Newcomer JW, Farber NB, Selke G, Melson AK, Jevtovic-Todorovic V, Olney JW. Guanabenz effects on NMDA antagonist-induced mental symptoms in humans. Soc Neurosci Abstr 1998;24:525.
53 Farber NB, Kim SH, Dikranian K, Jiang XP, Heinkel C. Receptor mechanisms and circuitry underlying NMDA antagonist neurotoxicity. Mol Psychiatry 2002;7:32–43.
54 Levanen J, Makela ML, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. Anesthesiology 1995;82:1117–25.
55 Handa F, Tanaka M, Nishikawa T, Toyooka H. Effects of oral clonidine premedication on side effects of intravenous ketamine anesthesia: A randomized, double-blind placebo-controlled study. J Clin Anesth 2000;12:19–24.
56 Kim SH, Price MT, Olney JW, Farber NB. Excessive cerebrocortical release of acetylcholine induced by NMDA antagonists is reduced by GABAergic

and α_2-adrenergic agonists. Mol Psychiatry 1999;4:344–52.
57 Lee YW, Yaksh TL. Analysis of drug interaction between intrathecal clonidine and MK-801 in peripheral neuropathic pain rat model. Anesthesiology 1995;82:741–8.
58 Jevtovic-Todorovic V, Wozniak DF, Powell S, Nardi A, Olney JW. Clonidine potentiates the neuropathic pain-relieving action of MK-801 while preventing its neurotoxic and hyperactivity side effects. Brain Res 1998;781:202–11.

Appendix 1

Precaution and Warning

During the same period in which the CRPS patients in this retrospective review were receiving ketamine therapy, other findings in animals and humans were being reported that have some bearing on the potential side effects of NMDA antagonists. NMDA antagonists including ketamine were found to trigger a dose-dependent neurotoxic reaction in the cingulate and/or retrosplenial cortices of adult rats when administered as a short-term treatment that entailed NMDA-receptor blockade (for a period of hours) [41–43]. This reaction was initially described as reversible vacuole formation. Research with phencyclidine and MK-801 revealed that a more prolonged NMDA-receptor blockade (for periods of 24–96 hours) resulted in irreversible neuronal degeneration and death in the retrosplenial cortex and other certain regions of the adult rat brain [44–46]. Whether the long-term administration of ketamine might also cause these same irreversible effects was not studied.

During this same period, different types of studies in humans were reported in the psychiatric literature in which volunteers received brief intravenous infusions of ketamine for the purpose of inducing transient symptoms classified as psychotic, as determined by psychiatric diagnostic rating scales [47–49]. Ketamine may induce psychotomimetic effects by disinhibiting certain excitatory transmitter circuits in the human brain [50]. Disinhibition of such circuits is thought to be the basis for the neurotoxic action of ketamine in the adult rat brain [50]. Consistent with this belief, several classes of drugs that restore inhibition to this circuitry also appear to prevent and/or reduce both neurotoxic effects in animals and psychotomimetic effects in humans [51–53]; and thus, these classes of drugs may be useful in providing a measure of protection in humans from the neurotoxic effects of NMDA antagonists (i.e., are neuroprotective). A more detailed review of this subject is available [50].

It also appears that one class of drugs used to prevent the side effects of NMDA antagonists may also be used to further facilitate the relief of neuropathic pain. For example, alpha-2-adrenergic agonists, such as clonidine, guanabenz, and dexmedetomidine, may not only protect against neurotoxic, psychotomimetic, and cardiostimulatory side effects [51,52,54–56], they may even enhance the pain-relieving action of NMDA antagonists [57,58].

Thus, to address the above safety concerns, and also to perhaps improve efficacy, we propose that a suitable neuroprotective agent be included whenever ketamine infusion therapy is undertaken for the purpose of treating CRPS.