Regarding Bell and Moore, Intravenous ketamine for CRPS: Making too much of too little? Pain 2010;150:10–11

To the Editor:

It is egregious enough that the reviewers got their facts wrong in their recent commentary published in *PAIN*. It is even worse that they then use their misstatements of fact to support their assertion that ketamine should not be a recognized option offered to patients with intractable CRPS that is unresponsive to other treatment modalities [1].

Intravenous ketamine is indicated by the Food and Drug Administration in the United States to control pain related to diagnostic and surgical procedures, and to supplement low-potency analgesic agents. IV ketamine has not been approved by the FDA to treat any specific medical condition. Ketamine has a safety record lasting over 30 years.

Schwartzman and colleagues published a randomized-controlled trial to determine the safety and efficacy of ketamine in the treatment of intractable CRPS on an outpatient basis [3]. We hope that the following information will help Bell and Moore to a better understanding.

1. The reviewers provide no support for their blanket assertion that the trial was not "convincingly blinded".
2. Blinding is in fact one of the strongest points about the Schwartzman paper. Midazolam was added as an active placebo to the control and ketamine groups. Patients with prior experience with ketamine were excluded from the study. Our experience at the International Research Foundation for RSD/CRPS after completing hundreds of 4-h infusions of midazolam and ketamine at sub-anesthetic doses (as used in the study at 25 mg/h) is that psychomimetic effects of ketamine are similar to midazolam and that patients cannot distinguish between the drugs at these low doses of ketamine.
3. A major concern expressed by the reviewers is the cost to the patient and healthcare system. The reviewers incorrectly stated that the research subjects in the Schwartzman study underwent a 4-h ketamine infusion daily for 10 weeks. The paper clearly states the 4-h infusions were carried out daily over a 10-day period. Furthermore, this was done in an outpatient setting. The published charge for a 4-h ketamine infusion at the Foundation's outpatient surgery center is $2500 US. The Schwartzman study showed that their maximum dose of 25 mg/h was too low a dose. Accordingly, we slowly increased the dose of ketamine from 60 up to 300 mg/h on an outpatient basis over a 3-day period. Over the past two years, we have completed over 300 infusions without any serious complications. These patients are averaging between 3 and 4 ketamine infusions per year and demonstrating substantial clinical improvements as measured by pain thresholds and video recordings of function before and after treatment.
4. The reviewers have recommended that Schwartzman and colleagues should have tried topical ketamine first rather than intravenous ketamine. This recommendation suggests little, if any, experience in treating patients with intractable CRPS. They point to a recent study where 0.5 ml of cream containing 10% ketamine was applied to the skin of patients with CRPS [2]. Conventional wisdom and clinical observation would suggest that the topical application of such a small amount of cream to the skin would not be practical as the majority of subjects in the Schwartzman study had widespread CRPS symptoms in multiple extremities (see Table 1 in Schwartzman et al. [3]). Although the topical ketamine study concluded there was a slight decrease in allodynia, there was no reduction in pain in the CRPS subjects. In contrast, Schwartzman and colleagues showed a statistically significant ($p < 0.05$) reduction in burning pain, pain when brushed or touched lightly and overall pain level in the subjects with CRPS in the most affected areas.

We joined the IASP believing that this organization would serve as an advocate for high quality science. The most disappointing and disturbing aspect of the Bell and Moore commentary is the apparent lack of accountability of the editorial staff of *PAIN* in publishing it. We agree that commentaries are the opinions of the authors. For those reasons standards should be implemented to assure the accuracy of what is published.

References

[1] Bell RF, Moore RA. Intravenous ketamine for CRPS: making too much of too little? Pain 2010;150:10–1.
[2] Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. Pain 2009;146:18–25.
[3] Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain 2009;147:107–15.

Anthony F. Kirkpatrick
International Research Foundation for RSD/CRPS, 1910 East Busch Blvd., Tampa, FL 33612, USA
Tel.: +1 813 995 5511
E-mail address: akirkpat@tampabay.rr.com

Timothy Lubenow
Department of Anesthesiology, Rush University Medical Center, 1653 W. Congress Parkway, Chicago, IL 60612, USA

doi:10.1016/j.pain.2010.08.019

Reply to Drs. Schwartzman, Kirkpatrick and colleagues

In our commentary, we sought to echo and emphasise the caution expressed by Schwartzman and colleagues in their report [1].

We inadvertently implied that the treatment in the Schwartzman study involved daily infusions of ketamine for 10 weeks, rather than daily treatment for 10 days, for which we apologize. The additional methodological details provided by Schwartzman and colleagues are helpful in judging the technique.

We fully agree with Drs. Kirkpatrick and Lubenow that Pain should function as an advocate for high quality science. Journals have a difficult task. Results of experimental or innovative therapies need to be published and scrutinised. On the other hand, we know that there are standards of evidence that have been set so that only those therapies with adequate supportive evidence of efficacy and safety go on to general use [2].

Those standards of evidence have been generated by the experience that good results in uncontrolled cohorts or non-randomised studies can be overturned in randomised studies and that even with randomised studies particular design characteristics bring with them a degree of bias – which is always in the direction of overestimating treatment effect. Among these characteristics is the issue of size: small studies can be wrong just by the random play of chance [3], and small studies can often distort results, as shown again recently [4], and Schwartzman and colleagues acknowledge this limitation [1].