



**TITLE: Intravenous Ketamine for the Treatment of Pain Syndromes: Clinical Effectiveness**

**DATE:** 07 June 2013

## **RESEARCH QUESTIONS**

1. What is the clinical effectiveness of intravenous (IV) ketamine for the treatment of recalcitrant chronic regional pain syndrome?
2. What is the clinical effectiveness of IV ketamine for the treatment of fibromyalgia?
3. What is the clinical effectiveness of IV ketamine for the treatment of reflex sympathetic dystrophy?

## **KEY MESSAGE**

One systematic review, two randomized controlled trials, and four non-randomized studies were identified regarding the clinical effectiveness of intravenous (IV) ketamine for the treatment of chronic regional pain syndrome. No health technology assessments, systematic reviews, randomized controlled trials, or non-randomized studies were identified regarding the clinical effectiveness of IV ketamine for the treatment of fibromyalgia or reflex sympathetic dystrophy.

## **METHODS**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and May 24, 2013. Internet links were provided, where available.

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The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

## **RESULTS**

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

One systematic review, two randomized controlled trials, and four non-randomized studies were identified regarding the clinical effectiveness of intravenous (IV) ketamine for the treatment of chronic regional pain syndrome. No health technology assessments, systematic reviews, randomized controlled trials, or non-randomized studies were identified regarding the clinical effectiveness of IV ketamine for the treatment of fibromyalgia or reflex sympathetic dystrophy. Additional references of potential interest are provided in the appendix.

## **OVERALL SUMMARY OF FINDINGS**

In most of the identified studies,<sup>1-5,7</sup> IV ketamine was effective at managing the pain experienced by patients with chronic regional pain syndrome (CRPS). Patients reported pain relief beyond the ketamine infusion period,<sup>3-5,7</sup> obtaining the greatest pain relief after one week,<sup>3</sup> with lasting pain relief reported up to six months.<sup>7</sup> Significant improvements in patient movement disorders were noted in one study,<sup>7</sup> but not in another.<sup>3</sup> However, Type 1 CRPS patients who had previously reported pain relief, completely lost this relief by week 12.<sup>3</sup> In addition, there were no gains in functional improvement.<sup>3</sup>

In contrast to the seemingly effective action of IV ketamine to provide pain relief, a study by Kiefer et al. reported that patients with refractory long-standing CRPS did not experience any pain relief when administered subanesthetic isomeric S(+)-ketamine.<sup>6</sup>

## REFERENCES SUMMARIZED

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-analyses

1. Azari P, Lindsay DR, Briones D, Clarke C, Buchheit T, Pyati S. Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review. *CNS Drugs*. 2012 Mar 1;26(3):215-28.  
[PubMed: PM22136149](#)

### Randomized Controlled Trials

2. 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 Dec 15;147(1-3):107-15.  
[PubMed: PM19783371](#)
3. Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain*. 2009 Oct;145(3):304-11.  
[PubMed: PM19604642](#).

### Non-Randomized Studies

4. Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. *Pain Med*. 2012 Feb;13(2):263-9.  
[PubMed: PM21939497](#)
5. Sigtermans M, Noppers I, Sarton E, Bauer M, Mooren R, Olofsen E, et al. An observational study on the effect of S(+)-ketamine on chronic pain versus experimental acute pain in Complex Regional Pain Syndrome type 1 patients. *Eur J Pain*. 2010 Mar;14(3):302-7.  
[PubMed: PM19540140](#)
6. Kiefer RT, Rohr P, Ploppa A, Nohe B, Dieterich HJ, Grothusen J, et al. A pilot open-label study of the efficacy of subanesthetic isomeric S(+)-ketamine in refractory CRPS patients. *Pain Med*. 2008 Jan;9(1):44-54.  
[PubMed: PM18254766](#)
7. Kiefer RT, Rohr P, Ploppa A, Dieterich HJ, Grothusen J, Koffler S, et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. *Pain Med*. 2008 Nov;9(8):1173-201.  
[PubMed: PM18266808](#)

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**APPENDIX – FURTHER INFORMATION:**

**Non-Randomized Studies – Pharmacodynamic Focus**

8. Dahan A, Olofsen E, Sigtermans M, Noppers I, Niesters M, Aarts L, et al. Population pharmacokinetic-pharmacodynamic modeling of ketamine-induced pain relief of chronic pain. *Eur J Pain*. 2011 Mar;15(3):258-67.  
[PubMed: PM20638877](#)
9. Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW. Pharmacodynamic profiles of ketamine (R)- and (S)- with 5-day inpatient infusion for the treatment of complex regional pain syndrome. *Pain Physician*. 2010 Jul;13(4):379-87.  
[PubMed: PM20648207](#)

**Review Articles**

10. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst Rev*. 2013;4:CD009416.  
[PubMed: PM23633371](#)
11. Niesters M, Dahan A. Pharmacokinetic and pharmacodynamic considerations for NMDA receptor antagonists in the treatment of chronic neuropathic pain. *Expert Opin Drug Metab Toxicol*. 2012 Nov;8(11):1409-17.  
[PubMed: PM22871026](#)
12. Sabia M, Hirsh RA, Torjman MC, Wainer IW, Cooper N, Domskey R, et al. Advances in translational neuropathic research: example of enantioselective pharmacokinetic-pharmacodynamic modeling of ketamine-induced pain relief in complex regional pain syndrome. *Curr Pain Headache Rep*. 2011 Jun;15(3):207-14.  
[PubMed: PM21360034](#)

**Additional References**

13. Henson P, Bruehl S. Complex regional pain syndrome: state of the art update. *Curr Treat Options Cardiovasc Med*. 2010 Apr;12(2):156-67.  
[PubMed: PM20842553](#)