Sigtermans MJ, van Hilten JJ et al. Ketamine produces effective and long-term relief in patients with Complex Regional Pain Syndrome Type I. Pain 2009;145:304-311.

Reviewed, no change to conclusions, February 2017

Design: Randomized clinical trial

Population/sample size/setting:

- 60 patients (48 women, 12 men, mean age 46) treated for CRPS-I at a university medical center in the Netherlands
- Inclusion criteria were CRPS-I by IASP criteria with a pain level of at least 5 on a scale from 0-10
- Exclusion criteria were age <18, pregnancy/lactation, serious medical disease (cardiovascular, renal, liver), use of strong opioids, or history of psychosis

Main outcome measures:

- All patients were admitted to the hospital for 5 days to receive intravenous infusions of study medication
- Randomization was to either the S(+) isomer of ketamine (n=30) or normal saline (n=30)
- Infusion rate of ketamine started at 1.2 mcg/kg/min (5 mg/h for a 70 kg person) and titrated to a maximum of 30mg/h, contingent on the pain response and on the emergence of side effects
- On the fifth day of the study, patients who had been randomized to placebo were offered the opportunity to receive ketamine in an open fashion
- Patients continued to be observed for 12 weeks; the primary outcome was the course of spontaneous pain on a scale from 0-10
- Several secondary measures were done: Radboud Skills Questionnaire (a Dutch language analog to the DASH, or Disabilities of Arm, Hand, and Shoulder for upper extremity function), a walking Ability Questionnaire, active range of motion by goniometry, touch threshold by Semmes-Weinstein monofilament, skin temperature by infrared thermometry, and volumetric measurements by the water displacement method
- All patients randomized to saline finished the IV infusions; 2 patients in the ketamine group withdrew on days 3 and 4 due to side effects
- At the end of the first week, the pain scores had decreased for the ketamine group (from 7.20 to 2.68) more than for the placebo group (from 6.87 to 5.45)
- Over the course of 12 weeks, the pain scores gradually increased in the ketamine group; at the end of 12 weeks, there was no longer a significant difference between ketamine and placebo (figure 3 appears to show scores close to baseline at week 12, but the scores are not reported in tabular form)
- None of the secondary measures improved significantly with ketamine
- Most patients had side effects; headache was similar in ketamine and placebo groups (37% vs. 33%), but other adverse effects were more frequent with

ketamine: nausea (63% vs.17%), vomiting (47% vs 10%), and psychomimetic effects (93% vs. 17%)

- 28 ketamine patients correctly guessed their treatment assignment; only 18 placebo patients correctly guessed theirs
- 20 placebo patients chose to take ketamine in an open label phase after the treatments were unblinded; these patients had a similar large decrease in pain after 1 week, and had a slow increase in pain scores over the following 12weeks; however, the increase was slower, and the final pain scores in the open label phase was lower than for the ketamine group in the double blind phase
- The duration of symptoms did not predict the pain response to ketamine; this varied from 0.1 to 31.9 years

Authors' conclusions:

- CRPS-I patients treated with individually titrated infusions of IV ketamine have a clinically relevant pain reduction lasting 11 weeks
- Side effects of ketamine infusion, though frequent, were generally mild and well tolerated
- Functional status was not improved by ketamine

Comments:

- Although every reasonable precaution was taken to reduce the risk of bias, the success of blinding in an experiment involving ketamine is likely to be poor
- The follow-up pain scores are displayed graphically in Figure 3 but not in tabular form; the 12 week pain scores can be estimated from the graph but precise numbers are preferable
- The apparently longer duration of pain relief during the open-label ketamine phase is difficult to explain, but may be partly influenced by high expectations which would arise from a willingness to enter the hospital twice for inpatient treatment
- The practicality of inpatient treatment with ketamine is likely to be limited, but the precautions taken with this trial were appropriate

Assessment: Adequate for evidence that inpatient infusion of IV ketamine reduces pain for up to 12 weeks, but that functional gains are not proven