Perez RS, Zuurmond WW, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. Pain 2003;102:297-307.

Design: Randomized clinical trial

Population/sample size/setting:

- 145 patients (49 men, 96 women, mean age 50) treated for CRPS-I at a university anesthesiology department in Amsterdam
- Criteria for CRPS were (1) presence of 4 of these 5 symptoms: unexplained diffuse pain, skin temperature differences between limbs, diffuse edema, difference in skin color between limbs, limited active range of motion; (2) aggravation of symptoms during or after exercise, (3) symptoms in an area larger than and distal to the primary injury
- CRPS had to be limited to 1 extremity, duration shorter than 1 year, with no prior treatment with N-acetyl cysteine (NAC) or dimethylsulfoxide (DMSO)
- Exclusion criteria were involvement of the contralateral limb, need for surgery on affected limb, and pregnancy

Main outcome measures:

- Patients were stratified according to treatment center and affected limb (upper or lower) for randomization
- Randomized to treatment for 17 weeks with either DMSO 50% cream (n=71) or 600 mg oral NAC three times daily (n=74)
- DMSO group was instructed to apply cream 5 times daily to affected area, in combination with 3 effervescent placebo tablets compounded to look and taste like NAC tablets
- NAC group was instructed to take 3 effervescent NAC tablets daily, and to apply placebo cream compounded to smell like DMSO
- Primary effect measure was the Impairment Level Sum Score (ISS), a composite of four aspects of CRPS: pain, volume, temperature, and active range of motion
- Several secondary effect measures were obtained, including EuroQol (a European quality of life measure), COOP/WONCA (a functional status instrument), SF-36, and questionnaires tailored to the affected upper or lower extremity
- Both groups showed decrease in ISS at 17 weeks from baseline; mean baseline ISS scores in DMSO and NAC groups were 29.42 and 29.08; mean ISS improvements were 9.05 and 8.31
- While these ISS scores were both statistical improvements from baseline, the DMSO and NAC groups did not differ from one another on the ISS improvements
- Subgroup analyses showed that DMSO was more effective than NAC for “warm” CRPS (the affected extremity is warmer than the unaffected) and NAC was more effective than DMSO for “cold” CRPS

- Numerous secondary measures were reported, one of which showed differences in favor of DMSO for disability level of the lower extremity

Authors' conclusions:

- DMSO and NAC are overall equally effective in treating CRPS-I
- Because significant differences in favor of DMSO over placebo have been reported in previous studies, and because DMSO is regarded as standard therapy for CRPS in the Netherlands, a decision was made not to apply a placebo control; a placebo explanation for the results cannot be excluded
- Treatment with DMSO for warm CRPS and with NAC for cold CRPS seem to be advisable

Comments:

- There is a very large number of analyses of the data, suggesting that many of them were exploratory in nature (or data mining)
- The primary outcome measure, the ISS, seems to be an impairment instrument which does not include allodynia and hyperpathia, and whose relevance (e.g., temperature and volume of the affected limb) to function is uncertain
- There was missing data for 19 patients in the first 17 weeks, and the methods for missing data could introduce bias; specifically, if no change or if a deterioration was reported, pretreatment scores were imputed at 17 weeks; ignoring deterioration could inflate the apparent treatment effect
- It is not clear whether the difference between warm and cold CRPS effects were pre-planned; this distinction between warm and cold subtypes seems to be common in the Dutch literature, but the data may be insufficient to support the recommendations for DMSO and NAC
- At least one of the placebo-controlled trials with DMSO (Zuurmond 1996) was inadequate for evidence and may have been biased; the lack of a placebo control makes the interpretation of the DMSO and NAC results uncertain

Assessment: Inadequate for evidence (lack of placebo comparison, questionable outcome measure, excessive numbers of secondary data analyses which may have been in search of statistical significance)