Reviewer's report

**Title:** Effect of Tadalafil on blood flow, pain, and function in chronic cold Complex Regional Pain Syndrome: A randomized controlled trial

**Version:** 1  **Date:** 20 May 2008

**Reviewer:** Robert Schwartzman

**Reviewer's report:**

**Major Compulsory Revisions:**
1. Adding PT to the methods is problematic. The reader does not know anything in regard to compliance, effort and skill of therapist. This needs to be addressed.


3. The data are sound. However, in pain studies a 30% increase over placebo is usually considered meaningful and 50% robust. The percent improvement of this study is only 15% and therefore this most important parameter of CRPS does not meet usual criterion (needs to be noted).

There is a large discrepancy between reported improvements in strength, activity levels and walking with documented improvement. The trend is there but the significance is not. Discussion of other factors that were not overcome such as peripheral or central sensitization or astrocytic secretion of inflammatory cytokines needs to be noted.

4. In general, this is a negative study. The study is based on an excellent idea, supported by recent experimental reperfusion work (Coderre and Bennett Pain 2004, 112(1-2):94-105). The quantitative approach to measure the chosen parameters is excellent.

**Minor Essential Revision**
1. A few grammatical mistakes in an otherwise well written paper.

**Discretionary Revisions**
1. Addition of physiologic data explaining cold CRPS (upregulation of adrenoreceptors in vasculature of affected vessels; change of small fiber innervation; changes in neuropeptide concentration (Albrecht et al Pain 2006, 120(3):244-66)

2. Better discussion of how changes in microenvironment (decreased blood flow) may increase pain by effects on TPRV receptors, free radical production, etc.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.