Reviewer's report

Title: Evidence based guidelines for complex regional pain syndrome type 1.

Version: 2 Date: 14 September 2009

Reviewer: Michael C Rowbotham

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- Major Compulsory Revisions

The text for the most part does not say how large the specific studies are. Most studies reviewed are small and very much under-powered, but it would help the reader to have at least the number enrolled. Also, if not all subjects were followed up, the number lost to followup should be stated.

No table summarizing the guide, just a bullet point list. For such a lengthy review, a proper summary table is essential. The table should provide a very brief rationale for each recommendation.

- Discretionary Revisions

1. Definition of CRPS taken from Stanton-Hicks 1995; not the more widely accepted one. This definition is vague and should not be further endorsed.

2. The authors should be commended on the thoroughness of their efforts. Literature search covers period 1980-2005 literature; ten plenary project group meetings, plus other group work. Formal endorsement was obtained in December 2006.

3. Another strength is the authors look at studies of CRPS prevention via guanethidine, calcitonin as primary prevention and also look at secondary prevention studies.

In some areas the lit review seems to be a review of the review. It is unclear how the reader is to interpret reviews of previously published reviews - does that mean the source papers for the older review were not accessed?

4. One open label study of high dose capsaicin under anesthesia (n=10); reference is incorrect - states 0.025% used (ref 21) from 1990

5. As shown below, the evidence base, even for pharmacological therapies is limited and problematic:

NSAID evidence is a single study of regional iv ketorolac

Severely limited database on opioids; one of the studies was of axillary plexus morphine which is not relevant to routine clinical practice.

Only two studies of local anesthetics; neither controlled and both in very small numbers of patients.

Sub-anesthetic ketamine seems encouraging; longer term data on only 20 of 33
patients in a retrospective study. Only 1 reference.
2 gabapentin RCTs, effect on pain but not sensory phenomena
No studies of TCAs
Multiple studies on DMSO as a free-radical scavenger; also N-acetylcysteine; evidence viewed as + with one study n=146. Is this therapy commercially available on only via a compounding pharmacy?
5 open studies on muscle relaxants; benzo and baclofen effective
Botox only 1 study, n=14 but only 4 were CRPS cases. Also cite two 'publications' stating botox never works or only for a short time.
One crossover RCT of IT baclofen. 2 studies total. n very small but some late followup data
All 3 steroid studies (systemic) +, only one controlled.
List 4 reviews of calcitonin tx; note conflicting conclusions, don’t review the primary papers though.
3 studies of bisphosphonates, all RCTs, usually high dose but tx may be very short, all +
calcium blockers 2 studies; don’t fully describe improvement.

6. The recommendations do not appear to consistently stem from the evidence reviewed. In some places it appears clear that the recommendation is based on the opinions of the working group and the authors acknowledge this, but in others such a statement is not present. Examples below:
Statement: "The project group asserts that pain medication should be administered in accordance with the WHO pain ladder up to and including step 2. Strong opioids should not be administered to this patient group." Such a statement has no basis in the studies reviewed.
The authors advocate ketamine without any recommendation for how to administer, monitor etc. It is hard to understand how a drug like ketamine, which does not have regulatory approval in any country for chronic pain and can have severe psychological side effects, would be advocated while opioids would be discouraged. Chronic administration of strong opioids has obvious and well-documented drawbacks, but at least the problem has been well studied in non-CRPS patient populations.
The authors recommend against botox despite essentially complete lack of evidence either way; don’t even recommend further study. Some justification should be provided.
Routine steroids also recommended against despite positive studies. Why?
Interestingly, percutaneous sympathetic blockade with local anesthetics appears to be discouraged despite the very widespread use of this treatment, while surgical sympathectomy appears to be encouraged. The text doesn't reconcile these conflicting recommendations, and also do not address the important issue of repeated sympathetic blocks - a widespread practice in the USA.
7. In summary, the authors have made a commendable effort to summarize the enormous, and mostly poor quality, literature on treatment of CRPS-1. The recommendations are limited in scope. The authors do not provide a practical algorithm for managing patients, which would require much additional effort by the working group.

No conflicts of interest to report.