Author's response to reviews

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

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Dear Editor-In-Chieff,

On behalf of my co-authors I would like to submit the revised revision of our manuscript entitled “Evidence based guidelines for complex regional pain syndrome type 1” (MS: 4828390682892911). We would like to thank the editorial board and prof. Rowbotham and prof. Albazaz for their thorough review and suggestions for improvement of the manuscript. We have addressed the issues in their review as good as possible, and have outlined our response to each point below. Of course we are willing to make further alterations if required.

Yours sincerely,

On behalf of all co-authors,
Roberto Perez

Answers to prof. Albazaz (reviewer 1),

We thank prof. Albazaz for his positive comments.

Major compulsory revisions:
- the authors should attempt an up to date search for relevant studies: we have updated our search using the search strategy as described in appendix 1 of our manuscript. 45 new studies were identified and described briefly in the discussion section, and articles were references under the heading “Articles not incorporated in these guidelines”. As the guideline development requires a formal procedure involving the participating professional organisations, these new articles could not be evaluated in the current guideline. This issue is discussed in this section.

Minor essential revisions:
- The sentence “A search string based…” was completed as requested.
- Results section: the total number of studies has been corrected to 94.
- Local anaesthetic section: type of local anaesthetic use was added and duration of follow-up was provided for references 16 and 17.
- The subanaesthetic dose of reference 18 of ketamine was added.
- The calcium channel blockers used in references 44 and 45 were specified.
- The sentence “…reduction of pain intensity…” has been changed into: “Pain intensity reduced by 2.4 cm on a visual analogue scale after six months in the group receiving spinal cord stimulation plus physiotherapy compared to the group receiving only physiotherapy [66]. At two years follow-up, pain decrease in the SCS group was 2.1 cm more than pain decrease observed in the physiotherapy group.”
- The study by Gschwind et al (reference 96) found no significant differences between perioperative guanethidine and placebo.
- Spelling and grammar were rechecked and corrected to our best knowledge.

Discretionary revisions:
- The sentence “Much remains to be learned…” has been removed as requested.
- As requested, the guidelines were presented in the form of a table (table 2).

Answers to prof. Rowbotham (reviewer 2),

Major compulsory revisions:
- The study sizes for the evaluated studies were added throughout the text as requested.
- A summary table of the recommendations, including a brief rational for the recommendations has been added (see table 2). As a consequence, the discussion section was altered substantially.

Discretionary revisions:
1. The definition of Stanton-Hicks was removed and replaced by the definition by Merskey and Bogduk (reference 1).
2-3. We thank professor Rowbotham for his positive appraisal
- As systematic reviews were considered to have the highest evidential strength, source papers to the reviews were not evaluated, unless to provide background information. This point has been clarified in the methods section.
4. The correct reference for high dose of capsaicin was added (reference 21).
5. We agree with prof. Rowbotham that the evidence base for the interventions discussed in this article is in general limited. We have tried to clarify this to the reader by describing the level of evidence for each conclusion, and provide directions in the recommendations for the interventions. In the present version, we have added a sentence to the method section explaining the relationship between level of evidence and the description of the recommendations.
- N-acetylcystein is available commercially (was initially sold under the brand name Fluimucil, but is currently out of patent). It can be obtained as a medical
product but also as a nutritional supplement.

6. Prof. Rowbotham is correct in stating that the recommendations do not always follow the available evidence. The recommendations are based on the combination of the available evidence and additional considerations related in part to Dutch perspectives with regard to organisation of health care and views of the task force and professional organisations. We have tried to point this out in the method section and the discussion.

- The recommendation regarding the use of the WHO pain ladder has been altered in “The project group is of the opinion that …” (see table 2).

- For the use of ketamine a sentence has been added in the additional considerations, stating that its use should be limited to the clinical setting.

- A section has been added to the discussion section specifically recommending further study into the uses of recommended and not recommended interventions, such as botuline toxin. This recommendation has been expressed for all interventions addressed in these guidelines, for reasons mentioned by prof. Rowbotham under point 5.

- The reasons for the task force not to recommend routine steroid use were based on the limited available evidence and side-effect profile of this intervention. This has been added to the additional considerations in table 2.

- The use of percutaneous sympathetic blockade can be considered for use in the present guidelines. Because of limited evidence, both definitive percutaneous sympathetic blockade as well as surgical sympathectomy are recommended to be used in the context of a study. Intravenous regional sympathetic blockade on the other hand is not recommended for treatment of CRPS-1 due to substantial negative evidence.

7. Again, we would like to thank prof. Rowbotham for his positive appraisal. As requested, we have added a practical algorithm based on these guidelines (see appendix 2).