Author’s response to reviews

Title: Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1

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Reviewer 1 Wouter Zuurmond

Major compulsory revisions

1. As asked we have extended our rationale and now mention the incidence of neuropathic pain in CRPS1 and included one extra reference (ref. Veldman et al 1993).
2. The reviewer doubts whether a complete reset occurs in our population after the intervention, thus questioning the relevance of our cross-over study design. Our results actually just show that. Figure 1 gives the VAS data, demonstrating that even in the group of patients first treated with gabapentin, the mean VAS returns to the starting value. We have added an explanation for this type of design in the patients and methods section (p.4-5) and the discussion section (p.13, line 9-24) already contained a large piece on the validity of cross-over designs in pain treatment trials, concluding that this design is not ideal in pain trials.
3. The reviewer raises an important point: before starting gabapentin treatment, one should consider the balance between advantages and disadvantages. This balance between side effects and pain relief is now discussed on p.13 and 14.

Minor essential revisions

1. Ref 1 was omitted and changed into Veldman et al (see literature ref. In the paper)
2. We now discuss our choice of chronic CRPS I patients on p.4/5. P.11 contains a description of follow-up of other CRPS indices. As we found no differences here, the discussion whether bedside evaluation of edema and skin temperature is reliable is perhaps not so relevant anymore. However, we based our choice of bedside evaluation on the paper by Oerlemans, Oostendorp, de Boo, Perez, and Goris (1999, see literature ref. in the manuscript), showing that indeed bedside evaluation correlates well with instrument measurements.
3. We now discuss the issue of blinding on p.14 line 10-14.
4. Table 1 is cited in the text on p. 9, which describes the randomisation. Table 1 is a numerative summary of this process. Mean and SD are added to the legends of table 2 and 3.

Reviewer 2 Miroslav Backonja

Major compulsory revisions

1. We thank the reviewer for his compliment that the study is well designed and carefully conducted with meticulous records.
2. The point about the cross-over design was also raised by reviewer 1. (Major point 2). We have added an explanation for this type of design in the patients and methods section (p.4-5) and the discussion section (p.13, line 9-24) already contained a large piece on the validity of cross-over designs in pain treatment trials, concluding that this design is not ideal in pain trials. Regarding the point that perhaps we should have known before, this phenomenon has only been observed in one other study (Moulin 1996) using morphine as active drug, which has more potential psychoactive properties.

3. We appreciate the offer by reviewer 2 to make a distinction for each treatment period, but we feel that this not justified. The study was powered for this number of patients, and drawing conclusions from one half, although tempting, would not be correct.

4. We have rephrased the section on p.4 into a less ambiguous one: all patients underwent the mentioned treatments.

5. We have rephrased the sentence 4 on p.4 as requested.

6. The sensibility and allodynia tests are described one page earlier. To ensure clarity we have now added 'see above' to this sentence.

7. Table 3 was provide with headings.

8. As asked we have now provided figure 1 as a line graph instead of the original bar graph.