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Letter to the Editor

Reply to Stausholm *et al.*'s letter to the editor regarding our published study entitled, "Effectiveness of low-level laser therapy in patients with knee osteoarthritis: a systematic review and meta-analysis"

Dear Editor,

First we would like to thank Stausholm *et al.* for their interest in our recent article on "Effectiveness of low-level laser therapy in patients with knee osteoarthritis: a systematic review and meta-analysis"[1]. The points raised by Stausholm *et al.* are focused on the methodological aspects of our paper. They use the A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool to assess our meta-analysis. We have carefully considered their concerns and offer a point-by-point response below. In addition, they provide an analysis using their own methodology involving adjustment for "baseline imbalance" in visual analog scale (VAS) pain scores that yields an overall positive effect of laser therapy for knee osteoarthritis. This methodology is not explained and involves transformation of the primary data in an unspecified manner. It is therefore not clear if this is a valid conclusion. Unless and until additional high quality studies are available, we continue to conclude that the best available current evidence does not support the effectiveness of low-level laser therapy for knee osteoarthritis.

AMSTAR validity tool: AMSTAR was based on an Overview Assessment Questionnaire[2,3] and a checklist by Sacks[4]. It consists of 11 items, each of which is categorized into a standardized set of four possible responses: "yes", "no", "cannot answer" or "not applicable". The items relate to a priori design, study selection and data extraction, the literature search, the status of publication (grey) literature, the list of included and excluded studies, study characteristics, appraisal of the scientific quality of studies, methods of combining studies, assessment of publication bias and reporting of conflicts of interest. Of note, there have been several recent papers summarizing the limitations of AMSTAR and potential solutions from the perspective of an assessor[5–7]. These suggestions for improvement are borne out in our response below.

1. *Was a priori design provided*? Stausholm *et al.* contend No.

Author's response: They are correct, although a detailed and comprehensive plan and search strategy was derived a priori and was followed for this meta-analysis, it was not explicitly provided in the publication.

2. *Was there duplicate study selection and data extraction*? Stausholm *et al.* contend No: "Two assessors independently selected the studies and extracted the data, however there was no consensus procedure for disagreements among them".

Author's response: In fact, the discrepancies between the two independent reviewers were resolved by consensus after discussion, and a third reviewer was consulted if necessary, which was mentioned clearly in the 'Quality assessment' section of our published meta-analysis.

3. *Was a comprehensive literature search performed*? Stausholm *et al.* contend Yes: "The literature search satisfies the criteria for a 'yes'. However, we strongly disagree that a comprehensive search was indeed performed: All Randomized Clinical Trials (RCTs) published before year 2000 were systematically excluded by their search criteria, thereby excluding at least three otherwise possible eligible RCTs. They also failed to identify the RCT by Hegedus published after year. All these four RCTs reported pain outcomes in favour of Low-Level Laser Therapy (LLLT) over placebo.

Author's response: There were several important reasons for excluding all the papers published before 2000. Although, Stausholm *et al.* contend that these three papers "reported pain outcomes in favour of LLLT over placebo", in fact, the study by Bulow *et al.*[8] did not support the effectiveness of LLLT over placebo. To quote the conclusion from the Bulow *et al.* abstract (full paper unavailable to us): "No significant differences in any of the effect variables were found between the two groups before, during or after treatment. With regard to the patients' overall assessment there was a clearly demonstrable positive effect of treatment in both groups. This is likely to be due to a placebo effect.". Importantly, the papers published before 2000 did not report sufficient details regarding the laser (characteristics of the LLLT device or the application technique) for inclusion in this meta-analysis. As to the Hegedus study, we in fact evaluated this paper and excluded it because they only reported mean values without standard deviations for outcomes, for example, VAS pain and range of motion (ROM); such data are not able to be combined for the meta-analysis. They provided error bars on their graphs but nowhere could we find an indication of the type of error bar they used (standard deviation, standard error, or 95% confidence interval). Thus, we excluded this paper from the meta-analysis.

4. *Was the status of publication* (*i.e., grey literature*) *used as an inclusion criterion*? Stausholm *et al.* comment No: "Non-English literature was excluded systematically".

Author's response: This question has been raised for many papers. The concern is that ignoring studies written in languages

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other than English could introduce a risk of bias. However, evidence shows that omitting non-English articles may have only a small effect, if any, on the conclusion of a systematic review[9]. For this reason, the recently published papers that highlight the limitations of AMSTAR have all suggested that this item should be modified to acknowledge that such exclusions have merit[5–7].

5. *Was a list of studies (included and excluded) provided*? Stausholm *et al.* comment No.

Author's response: Although we did not include a list of studies that were excluded, we did include a complete list of studies that were included. At the current time, primarily only Cochrane reviews provide the list of excluded studies.

6. *Were the characteristics of the included studies provided*? Stausholm *et al.* comment Yes.

Author's response: We agree.

7. *Was the scientific quality of the included studies assessed and documented*? Stausholm *et al.* contend No. “The quality of the included trials was assessed, however the choice of assessment tool was not stated/provided prior to the search”.

Author's response: Burda *et al.*[5] have pointed out that the meaning of the phrase ‘a priori methods of assessment’ is unclear in the AMSTAR instructions. In our opinion, if one study does not meet the criterion of item 1, then it cannot meet the criterion of item 7. Thus, these AMSTAR items are not independent on one another. This is also an important flaw of the current AMSTAR criteria.

8. *Was the scientific quality of the included studies used appropriately in formulating conclusions*? Stausholm *et al.* contend Yes: “The scientific quality of the included studies did not affect the conclusion”.

Author's response: Because all the studies we included were of satisfactory scientific quality, they were all included and responsible for the overall conclusion of no effect of LLLT for knee Osteoarthritis (OA) pain.

9. *Were the methods used to combined the findings of the studies appropriate*? Stausholm *et al.* contend No: “The clinically appropriateness of combining the trials in the different subgroups was not considered. Huang and colleagues subgrouped the trials by adherence or non-adherence to the World Association of Laser Therapy (WALT) dosage recommendations. However, their subgrouping was incorrect and this was indicated by a high heterogeneity in the optimal dose subgroup in Huang and colleagues analysis. Correcting this misclassification eliminated completely this heterogeneity”.

Author's response: Although Stausholm *et al.* mention the recommended dosage of LLLT by WALT, they have referred only to the required energy (dosage) needed to do the treatment. What they did not mention is that the WALT dosage recommendations also assign points on the basis of treated sites. This latter criterion dictated the subgroupings in an appropriate way in our meta-analysis. They contend that the study by Gur *et al.* should be included while that by Tascioglu *et al.* should not. However, according to the WALT guidelines, when a 904 nm light is used, an appropriate treatment strategy involves the application of a minimum of 1 J to each of 4–6 treatment points. Although Gur *et al.* used a 904 nm light, they only applied it to two treatment points; thus we assigned the study by Gur *et al.* to the non-optimal dosage subgroup based on this study characteristic. According to the WALT guidelines, when a 830 nm light is used, an appropriate treatment strategy involves the application of a minimum of 4 J to each of 3–6 treatment points. The study by Tascioglu *et al.* used a 830 nm light and applied 3 J to three treatment points for a total of 10 visits so we assigned this study to the optimal treatment subgroup.

Stausholm *et al.* suggest that correction of the ‘misclassification’ could completely eliminate the heterogeneity. We disagree. The high heterogeneity of the studies in our meta-analysis could be caused by many other factors, such as the different devices used, the different patient populations, and the study of different stages of disease.

10. *Was the likelihood of publication bias assessed* Stausholm *et al.* contend No.

Author's response: The total number of the included studies was nine, which is a relatively small number. Usually for meta-analysis involving fewer than 10 studies, assessment of publication bias using funnel plots or statistical tests is not appropriate due to small sample effects[10].

11. *Was the conflict of interest included*? Stausholm *et al.* contend No: “It was not reported for included trials. Also, we challenge the statement by Huang *et al.* of having no competing interests to disclose, since the senior author has declared several conflicts of interest in papers related to research on pharmaceutical painkillers, which are competitors to LLLT”.

Author's response: Conflicts of interest were not explicitly described in our publication. For the included trials, five of them reported clearly that they did not have potential conflicts of interest[11–15], while the others did not mention the issue of conflicts of interest in their paper[16–19]. The senior author of our paper, Dr Virginia Kraus, reasserts that she has no conflicts of interest related to this meta-analysis. Her work has focused on basic science and translational research in osteoarthritis. She has assisted with or consulted for trials of both pharmacological and non-pharmacological agents but has not participated in laser therapy trials, or owned stock in or directed laser therapy companies. Our own group has published a subsequent meta-analysis[20] concluding that evidence exists for a beneficial effect of laser therapy for back pain. Thus, our group has no a priori bias for or against laser therapy. Based on the different results in knee and back pain, we would conclude that each source of pain and joint site appears to be different and needs to be studied separately and objectively to determine what really works for osteoarthritis. With respect to potential conflicts of interest, we noticed that at least two of the authors of this letter to the editor, Drs Bjordal and Joensen, are involved in laser therapy trials (NCT02304003 and NCT02749929, Dr Bjordal is principal investigator of both); one of these trials is actively recruiting participants, yet these authors have declared they have no conflicts of interest with respect to this letter to the editor. Moreover, we find that Professor Jan Magnus Bjordal has consistently criticized negative results drawn by systematic reviews[21,22] or randomized clinical trials[23,24] of LLLT. In particular, we are concerned with the potential conflicts of interest related to their letter to the editor, especially given the fact that one author (Dr Bjordal) is a co-author on a recent white paper concerned with the means to “establish insurance reimbursement for photobiomodulation procedures” (http://www.naalt.org/index.php/whitepapers/22-insurance-reimbursement-whitepaper).

We contend that it is important to maintain an objective viewpoint when studying any therapy, and most especially therapies for which subject blinding is very difficult or impossible, such as laser therapy.

VAS pain sensitivity analysis

Author's response: Stausholm *et al.* contend that "results changed fundamentally" "by applying a different valid statistical analysis approach to the very same trials" although details of the methodology are not provided. Specifically, they report adjusting the "baseline imbalance" in VAS pain across studies. First, Stausholm *et al.* did not disclose how they adjusted the "baseline imbalance" therefore, it is not possible to assess whether their analysis is valid. Second, within each study, baseline VAS scores were similar for the treated and placebo groups since all nine studies were randomized; therefore, it should not be necessary nor appropriate to correct for baseline VAS since the meta-analysis is dependent upon the mean difference between groups at the study end. Third, they assert that they were able to reduce the heterogeneity to 0%, thereby proving that their results were more robust. Actually, it is very easy to decrease heterogeneity by pooling studies with similar results and ignoring negative studies.

In conclusion, we cannot agree that Stausholm *et al.* followed the AMSTAR guidelines; guidelines which they themselves have used to suggest that there were flaws in our meta-analysis.

Author contribution

The first author drafted the original reply and the corresponding author revised it.

Conflict of interest

The authors certify that we have no commercial associations that might pose a conflict of interest in connection with this article.

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