PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Low Level Light Therapy/Photobiomodulation for Diabetic Peripheral Neuropathy: Protocol of a Systematic Review and Meta-analysis
AUTHORS	Wang, Jiayou; Zouqin, Huang; Deng, Haiping; Zhao, Ling; Hongyong, Deng; Liu, Jianping; Shen, Xueyong; Cheng, Ke

VERSION 1 – REVIEW

REVIEWER	MALBERT, Charles-Henri INRAE, Aniscan
REVIEW RETURNED	06-Mar-2022

GENERAL COMMENTS	This manuscript described a study protocol for a systematic review and meta-analysis about the efficacy of laser therapy for diabetic peripheral neuropathy. It will use state of the art software tools for meta-analysis e.g. RevMan/Grade approach. The goals are clearly described per Grade approach. It will be an important addition to literature that consist of two former reviews but with less patients and fewer laser types. • The inclusion of type 1 and type 2 diabetes is surprising and needs to be discussed since laser therapy is primarily targeted on DT2. • The confounder effect of additional therapeutics is not clearly described and need further explanation on how it will be handle. • Support subsection (sources, sponsor, role of sponsor) is not present on page 8 (as indicated in PRISMA report form) and was not clearly indicated.

REVIEWER	Selvarajah, Dinesh University of Sheffield, Department of Human Metabolism
REVIEW RETURNED	13-Mar-2022

GENERAL COMMENTS	This manuscript describes a methodology to conduct a systemic review to examine the benefit and harm of laser therapy in DPN. LAser therapy is an esotheric treatment and it would benefit the readership to have a brief background on laser therapy and potential mechanisms of action for this approach. There appears to be many different approaches that will be assessed and the scientific validity of examine these together remain unclear. The main outcome is a composite of several neuropathy assessment tools each with unique properties. It is not clear how these will be combined to serve as a primary outcome. Moreover it is probably not valid to combine a screening tool with a diagnostic instrument and a generic pain intensity score. The is little rationale for this approach. Finally, the findings of previous studies need a more in depth discussion of findings and how the present systematic review is informed by the past studies and why it is justified. Has there been

	many new studies since the last review to warrant a further examination? Minor comments: There are several factual errors in the introduction which needs to be addressed along with missing references. E.g. the biggest risk factor of DPN are chronic hyperglycaemia and diabetes duration may be true for T1DM but not for T2DM. NSAIDs may be commonly used to treat DPN but these agents have not been 'proven' to be effective.

REVIEWER	Bansal, Dipika National Institute of Pharmaceutical Education and Research
REVIEW RETURNED	16-Mar-2022

GENERAL COMMENTS

Page &Line No.	Comments
Abstract	
Page 2 & Line No.48	Method need to be revised to include outcomes, sensitivity analysis, cumulative analysis. The method should also include test for publication bias
Introduction	
Page 3	Kindly clarify whether it is Diabetic peripheral neuropathy or painful diabetic neuropathy (PDN)
Page 3	Kindly clarify whether laser therapy is used for pain or something else.
Page 3&Line No 51	Incorrect Abbreviation (NSADs). Kindly Correct it.
Page 4&Line No.3	Kindly reform the sentence “The mechanism of laser action is not completely clearly”.
Objective	
Page 4 & Line No.21	Kindly revise the objective to make it more outcome oriented
Methods	
Page 4	Kindly mention the guidelines which would be followed while performing the study.
Page 4	The Comparator group is not mentioned in the methodology.
Page 5& Line No.46	Kindly clarify who will translate the studies in Chinese language.
Page 5 & Line No.46	Kindly mention the date of coverage of articles while performing the search.

	Page 6& Line No.6	Kindly clarify the role of each author or investigator
	Page 6& Line No.9	Kindly clarify in case of disagreements how independent review will be done
	Page 6& Line No.15	Kindly mention whether data extraction is paper based or directly entered into Microsoft excel spreadsheet
	Page7&Line No. 3	Kindly change “continues” to “continuous”.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Charles-Henri MALBERT, INRAE

Comments to the Author:

This manuscript described a study protocol for a systematic review and meta-analysis about the efficacy of laser therapy for diabetic peripheral neuropathy. It will use state of the art software tools for meta-analysis e.g. RevMan/Grade approach. The goals are clearly described per Grade approach. It will be an important addition to literature that consist of two former reviews but with less patients and fewer laser types.

• The inclusion of type 1 and type 2 diabetes is surprising and needs to be discussed since laser therapy is primarily targeted on DT2.

Response: Many thanks for your helpful comments. We agree that many laser/light therapies are targeted on DT2, but there are also some studies involving patients with type 1 diabetes. The previous two systematic reviews on the similar topic included several studies of patients with both types. [Robinson 2017, M A 2019] We believe the mechanisms of DPN from both types of diabetes are similar. In order to study the benefit and harm of laser therapy on DPN more comprehensively, we try to include related studies as broadly as possible. In order to determine the difference of the effect of laser/light on either type, we plan to do a subgroup analysis if the data allow us to do so. The subgroup analysis has been mentioned in ‘METHOD AND ANALYSIS-Data collection and analysis - Subgroup analysis’ section.

Reference

M A, Ummer VS, Maiya AG, Hande M. Low level laser therapy for the patients with painful diabetic peripheral neuropathy - A systematic review. Diabetes & metabolic syndrome. 2019;13(4):2667-70.

Robinson CC, Klahr PDS, Stein C, Falavigna M, Sbruzzi G, Plentz RDM. Effects of monochromatic infrared phototherapy in patients with diabetic peripheral neuropathy: a systematic review and meta-analysis of randomized controlled trials. Braz J Phys Ther. 2017 Jul-Aug;21(4):233-243.

• The confounder effect of additional therapeutics is not clearly described and need further explanation on how it will be handle.

Response: Thank you for your useful comments. In order to eliminate confounding effects, we will only include RCTs that used the same additional therapeutics (usually conventional treatment as co-intervention) in each group. That is, we will compare true LLLT vs. sham LLLT, LLLT vs. no additional treatment, LLLT vs. other specific treatment, or LLLT plus another treatment (usually conventional treatment) vs. the same treatment alone.

We have now added the above comparisons in 'METHOD AND ANALYSIS - Type of intervention' section.

• Support subsection (sources, sponsor, role of sponsor) is not present on page 8 (as indicated in PRISMA report form) and was not clearly indicated.
Response: Thanks for your suggestion. We have now added sources, sponsor, role of sponsor in the item of 'Funding' in our manuscript as below. The statement also follows the preferable wording example given by BMJ open in stating the support of the work.

"This work is supported by funding from the National Key R&D Program of China (grand number 2019YFC1709803) and National Natural Science Foundation of China (grand number 81873183). Jian-Ping Liu was partially supported by the NCCIH grant (AT001293 with sub-award No. 020468C). The funder had no role in study design, data collection and analysis, interpretation of result, or writing the manuscript."

Reviewer: 2
Dinesh Selvarajah, University of Sheffield
Comments to the Author:
This manuscript describes a methodology to conduct a systemic review to examine the benefit and harm of laser therapy in DPN. LAser therapy is an esotheric treatment and it would benefit the readership to have a brief background on laser therapy and potential mechanisms of action for this approach. There appears to be many different approaches that will be assessed and the scientific validity of examine these together remain unclear.
Response: Many thanks for your constructive comments. We have now added a brief background on low level laser therapy (LLLT)/photobiomodulation and potential mechanisms of action for this approach in the 4th paragraph in 'INTRODUCTION' section. We have now focused on visible (especially red) and infrared lights, because they are the main lights used in LLLT/photobiomodulation, and researches have showed their effects in pain inhibition and treating pathological conditions associated with the nervous system in DPN. More detailed statements have been added in 'INTRODUCTION' section and has also been clarified in 'METHOD AND ANALYSIS - Type of intervention' section.

The main outcome is a composite of several neuropathy assessment tools each with unique properties. It is not clear how these will be combined to serve as a primary outcome. Moreover it is probably not valid to combine a screening tool with a diagnostic instrument and a generic pain intensity score. The is little rationale for this approach.
Response: Thanks for your very helpful comments. We have now changed our main outcome to "change in pain measured using a validated scale". The reason is that pain is the main symptom in DPN patients, especially for the painful DPN, so pain is one of the main target in DPN management. In addition, previous research found that one of the main functions of low level laser therapy/photobiomodulation for DPN is relieving DPN-related pain. [Chatterjee 2019, de Freitas 2016, da Silva Oliveira 2018]
But we want to keep global symptom improvement as one of our secondary outcomes, because this outcome is clinically relevant and many studies measured this outcome, although with different instruments, and it may reflect the global effect of a treatment. We are aware that it's inappropriate to include generic pain intensity score in this outcome, so we now remove it from this section. As you mentioned, MNSI and MDNS are screening and diagnostic instruments for DPN, however, we found that they were also recommended as outcome measures for DPN [merkies 2006]. TCSS, another diagnostic instrument, has been proved as valid in reflecting the presence and severity of DPN [Bril V 2002]. These instruments as well as NSS (neuropathy symptom score) assess similar components of

neuropathic symptoms including presence of different pains (e.g., burning, tingling), dysesthesias (e.g., numbness), or abnormal nerve reflex, vibration perception and termal discrimination. Thus, to some extent, they could be combined to get a pooled effect of a treatment for the global symptom of DPN. The above instruments are also included under the 'symptom quality and severity' outcome in a recent Cochrane systematic review on DPN. [Rolim 2019] For the RCTs that assessed the same outcome using continuous data (i.e., global symptom improvement) by various instruments, we would use standardized mean difference (SMD) following the instruction of the Cochrane Handbook Chapter 6.5.1.2.

In addition, in case the global symptom outcome is reported as dichotomous data, we have added a description on how to deal with dichotomous outcome, following the method in another Cochrane review. [Chen 2013]

Reference

Chatterjee P, Srivastava AK, Kumar DA, Chakrawarty A, Khan MA, Ambashtha AK, et al. Effect of deep tissue laser therapy treatment on peripheral neuropathic pain in older adults with type 2 diabetes: a pilot randomized clinical trial. BMC geriatrics. 2019;19(1):218.

de Freitas LF, Hamblin MR. Proposed Mechanisms of Photobiomodulation or Low-Level Light Therapy. IEEE J Sel Top Quantum Electron. 2016 May-Jun;22(3):7000417.

da Silva Oliveira VR, Cury DP, Yamashita LB, Esteca MV, Watanabe IS, Bergmann YF, et al. Photobiomodulation induces antinociception, recovers structural aspects and regulates mitochondrial homeostasis in peripheral nerve of diabetic mice. Journal of biophotonics. 2018;11(9):e201800110.

Merkies IS, Lauria G. 131st ENMC international workshop: selection of outcome measures for peripheral neuropathy clinical trials 10-12 December 2004, Naarden, The Netherlands. Neuromuscular disorders : NMD. 2006;16(2):149-56.

Bril V, Perkins BA. Validation of the Toronto Clinical Scoring System for diabetic polyneuropathy. Diabetes care. 2002;25(11):2048-52.

Rolim LC, da Silva EM, Flumignan RL, Abreu MM, Dib SA. Acetyl-L-carnitine for the treatment of diabetic peripheral neuropathy. The Cochrane database of systematic reviews. 2019;6(6):Cd011265.

Chen W, Zhang Y, Li X, Yang G, Liu JP. Chinese herbal medicine for diabetic peripheral neuropathy. Cochrane Database Syst Rev. 2013 Oct 6;(10):CD007796

Finally, the findings of previous studies need a more in depth discussion of findings and how the present systematic review is informed by the past studies and why it is justified. Has there been many new studies since the last review to warrant a further examination?

Response: Thanks for your comments. Yes, after literature search, we found 6 more new English-language trials and about additional 6 Chinese-language trials on this topic. The previous two systematic reviews [Robinson 2017, M A 2019] each only included 6 English language studies. Among the 6 studies included in the 2019 review, 3 were non-RCTs. In addition, both reviews were with some methodological defects, and their conclusions were inconsistent with each other. Thus, it's time for an update of the topic by updating with new trials with sound methodology. This will produce more rigorous and generalized evidence. More detailed information has been included in the discussion section and our cover letter to editors.

Reference

Robinson CC, Klahr PDS, Stein C, Falavigna M, Sbruzzi G, Plentz RDM. Effects of monochromatic infrared phototherapy in patients with diabetic peripheral neuropathy: a systematic review and meta-analysis of randomized controlled trials. Braz J Phys Ther. **2017** Jul-Aug;21(4):233-243.

M A, Ummer V S, Maiya AG, Hande M. Low level laser therapy for the patients with painful diabetic peripheral neuropathy - A systematic review. Diabetes Metab Syndr. **2019** Jul-Aug;13(4):2667-2670

Minor comments:

There are several factual errors in the introduction which needs to be addressed along with missing references. E.g. the biggest risk factor of DPN are chronic hyperglycaemia and diabetes duration may be true for T1DM but not for T2DM. NSAIDs may be commonly used to treat DPN but these agents have not been 'proven' to be effective.

Response: Many thanks for pointing out our errors. We found recent evidence indicating that **age**, diabetes duration and glycosylated hemoglobin probably be significant risk factors for diabetes of both types.[Liu 2019, Papanas 2015] We have now revised our manuscript based on your advice. As suggested, we have also removed “NSAIDs”, and revised the paragraph according to recent guidelines.

Reference

Liu X, Xu Y, An M, Zeng Q. The risk factors for diabetic peripheral neuropathy: A meta-analysis. PloS one. 2019;14(2):e0212574.

Papanas N, Ziegler D. Risk Factors and Comorbidities in Diabetic Neuropathy: An Update 2015. Rev Diabet Stud. 2015 Spring-Summer;12(1-2):48-62.

Reviewer: 3

Dr. Dipika Bansal, National Institute of Pharmaceutical Education and Research

Comments to the Author:

The protocol requires some revisions before publication. The comments for the protocol is attached.

Response: Many thanks for your detailed comments listed in below table. Please find below our response to each of your comments.

Page & Line No.	**Comments**	**Response**
Abstract		
Page &Line No.	Method need to be revised to include outcomes, sensitivity analysis, cumulative analysis. The method should also include test for publication bias	We have now revised to include primary outcomes, sensitivity analysis, cumulative analysis, and publication bias in Abstract.
Introduction		
Page 3	Kindly clarify whether it is Diabetic peripheral neuropathy or painful diabetic neuropathy (PDN)	Thanks for your suggestion. We have clarified in the 'Types of studies' and 'Types of population' that we will include RCTs/ participants of DPN (diabetic peripheral neuropathy). We will not include RCTs of painful diabetic neuropathy alone, because peripheral neuropathy can also manifest with painless symptoms [Kaur S 2011, Shillo P_2019], painful DN is one of the forms of DPN. We aim to evaluate the effect of low level laser therapy(LLLT) on all DPN related symptoms including numbness and other abnormal sensations which will be assessed in global symptom scales and other nerve functional scales. **Reference** Kaur S, Pandhi P, Dutta P. Painful diabetic neuropathy: an update. Annals of neurosciences. 2011;18(4):168-75.

		Shillo P, Sloan G, Greig M, Hunt L, Selvarajah D, Elliott J, et al. Painful and Painless Diabetic Neuropathies: What Is the Difference? Current diabetes reports. 2019;19(6):32.
Page 3	Kindly clarify whether laser therapy is used for pain or something else.	Low level laser therapy is used for both pain and other symptoms related with DPN. We have mentioned in paragraph 4 under INTRODUCTION that "low level laser, has also been used to treat DPN due to its function in alleviating pain and improving lower limbs sensation." and “On the tissue level, LLLT has been used to inhibit pain and pathological conditions associated with the nervous system. It exerts potent anti-inflammatory effects in the peripheral nervous system and promotes functional recovery and regeneration of peripheral nerves after injury, also in DPN.”
Page 3&Line No 51	Incorrect Abbreviation (NSADs). Kindly Correct it.	We have now removed “NSAIDs” according to other peer-review comments.
Page 4&Line No.3	Kindly reform the sentence “The mechanism of laser action is not completely clearly”.	We have removed this sentence according to the response to other comments.
Objective		
Page 4 & Line No.21	Kindly revise the objective to make it more outcome oriented	We have revised to make objective more outcome oriented.
Methods		
Page 4	Kindly mention the guidelines which would be followed while performing the study.	We have added “We will use standard methodological procedures following Cochrane Handbook.” at the first line under METHOD section.
Page 4	The Comparator group is not mentioned in the methodology.	We have now added comparator groups.
Page 5& Line No.46	Kindly clarify who will translate the studies in Chinese language.	We have added sentence under ‘Search methods for identification of studies’ section as below: "The studies in Chinese language will be translated by JYW and checked by KC."
Page 5& Line No.46	Kindly mention the date of coverage of articles while performing the search.	We have mentioned that "We will search, with no time and language restrictions..." We have now also added that "The last search date will be the date before the submission of the full review. "

Page 6& Line No.6	Kindly clarify the role of each author or investigator	We have clarified as suggested in 'Study selection' section.
Page 6& Line No.9	Kindly clarify in case of disagreements how independent review will be done	We have clarified as below. "In case of disagreement, a third author (KC) will make the final decision on the study selection."
Page 6& Line No.15	Kindly mention whether data extraction is paper based or directly entered into Microsoft excel spreadsheet	We have added that ".....outcomes using a structured data extraction form and enter into Microsoft excel spreadsheet....."
Page7&Line No. 3	Kindly change "continues" to "continuous".	We have revised as suggested

VERSION 2 – REVIEW

REVIEWER	Selvarajah, Dinesh University of Sheffield, Department of Human Metabolism
REVIEW RETURNED	15-Jun-2022

GENERAL COMMENTS	The authors have responded to the reviewers comments adequately. Advice caution in misinterpreting study/review recommendation: MNSI and MDNS are screening and diagnostic instruments for DPN, however, we found that they were also recommended as outcome measures for DPN [merkies 2006]. TCSS, another diagnostic instrument, has been proved as valid in reflecting the presence and severity of DPN [Bril V 2002] Merkies et al acknowledge that MNSI and MDNS are screening and diagnostic tools for DPN and crucially the 'choice of an outcome measure will depend on the specific questions being asked in a particular study (e.g. trial evaluating the efficacy or safety of a new therapeutic drug versus epidemiological follow-up study).' These symptom/clinical examination construct scales are dependent on stage of disease severity and acknowledged to be unresponsive i.e. better suited to epidemiological studies rather than assessing therapeutic efficacy of new drug therapies. For assessing therapeutic efficacy the IASP IMMPACT consensus recommendation for outcome measures is most widely used (Dworkin R 2012 et al Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations).

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Dinesh Selvarajah, University of Sheffield
Comments to the Author:
The authors have responded to the reviewers comments adequately. Advice caution in misinterpreting study/review recommendation:

MNSI and MDNS are screening and diagnostic instruments for DPN, however, we found that they were also recommended as outcome measures for DPN [merkies 2006]. TCSS, another diagnostic instrument, has been proved as valid in reflecting the presence and severity of DPN [Bril V 2002]

Merkies et al acknowledge that MNSI and MDNS are screening and diagnostic tools for DPN and crucially the 'choice of an outcome measure will depend on the specific questions being asked in a particular study (e.g. trial evaluating the efficacy or safety of a new therapeutic drug versus epidemiological follow-up study).'
These symptom/clinical examination construct scales are dependent on stage of disease severity and acknowledged to be unresponsive i.e. better suited to epidemiological studies rather than assessing therapeutic efficacy of new drug therapies. For assessing therapeutic efficacy the IASP IMMPACT consensus recommendation for outcome measures is most widely used (Dworkin R 2012 et al Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations).
Response: Many thanks for reviewer's comments. We are sorry to have misunderstood and misinterpreted review recommendation from Merkies 2006 article. We agree that the symptom/clinical examination constructed scales are not suitable in evaluating therapeutic efficacy of an active treatment in RCT design, so we excluded the emanation scales from the symptom outcome and added more validated DPN symptom scales. We also stated the reason for excluding these examination scales in the main text. We greatly appreciate reviewer for providing such professional and helpful comments which will improve our manuscript to a level suitable for publication.

Reviewer: 2
Competing interests of Reviewer: none