PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Acupuncture therapies for postherpetic neuralgia:a protocol for a systematic review and Bayesian network meta-analysis
AUTHORS	Bian, Zhiyuan; Yu, Jie; Tu, Mingqi; Liao, Binjun; Huang, Jingmei; Izumoji, Genki; Sun, Ruohan; Xu, Yunyun; Jiang, Yongliang; He, Xiaofen; Fang, Jian-Qiao

VERSION 1 – REVIEW

REVIEWER	Giovanardi, Carlo Associazione Medici Agopuntori Bolognesi - AMAB, Acupuncture
REVIEW RETURNED	14-Oct-2021

GENERAL COMMENTS	Making reference to the types of control groups you mention (Studies using either conventional medication, sham-acupuncture or placebo in the control groups, as well as studies comparing different types of acupuncture therapies will be included), I'd like to comment as follows. According to the widely recognized principle that no skin stimulation is inert, 'sham acupuncture' cannot be inert, since any skin stimulation brings about central and peripheral responses 1 and the same applies to whatever form of placebo acupuncture involves stimulation of the skin. According to TCM, there are no points with no function, the whole skin being able to trigger physiological responses, as confirmed by the functions of the cutaneous regions called pí bù in Chinese. If sham points located far away from traditional acupuncture points and with no known function are used, physiological effects are observed. A light touch of the skin stimulates mechanoreceptors coupled to slow conducting unmyelinated (C) afferents; activity in these afferents has been suggested to induce a 'limbic touch' response resulting in emotional and hormonal reactions. Control procedures which are meant to be inert are likely to activate these afferents 2. In conclusion, comparison of verum acupuncture vs sham or placebo acupuncture may unnecessarily confuse rather than clarify the interpretation of the effects. Sham and placebo acupuncture should not be used as control groups. More positive and reliable outcomes from the administration of acupuncture can be expected if acupuncture is compared only with usual care 3. I do hope that my comments can provide a useful insight into acupuncture.

	References 1. Birch S. A review and analysis of placebo treatments, placebo effects, and placebo controls in trials of medical procedures when sham is not inert. J Altern Complement Med. 2006;12(3):303-10. 2. Lund I, Lundeberg T. Are minimal, superficial or sham acupuncture procedures acceptable as inert placebo controls? Acupunct Med. 2006;24(1):13-5. 3. Zheng CH, Huang GY, Zhang MM, Wang W. Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: a systematic review and meta-analysis. Fertil Steril. 2012;97(3):599-611.

REVIEWER	Lin, Guohua Guangzhou University of Chinese Medicine
REVIEW RETURNED	25-Nov-2021

GENERAL COMMENTS	This study protocol a systematic review and Bayesian network meta-analysis about comparisons of the efficacy between different acupuncture therapies for PHN. I have three comments below. 1. The purpose of the research should be clarified. As far as we know, current acupuncture applications and research mainly focus on traditional manual acupuncture and electro-acupuncture, is there any evidence that other acupuncture methods (such as those listed by the author) may have significant effects on PHN? 2. Research results should be clearly defined. The primary outcome described in this protocol is measurements of pain intensity. As a variety of measurement methods were listed in the protocol, the evaluating approach should be clear. 3. PRISMA flow chart is suggested to be presented in this protocol.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1（Dr. Carlo Giovanardi, Associazione Medici Agopuntori Bolognesi - AMAB, Federazione Italiana delle Società di Agopuntura -FISA）

Thank you very much for this valuable and helpful comment.
Response to comment：Comparison of verum acupuncture vs sham or placebo acupuncture may unnecessarily confuse rather than clarify the interpretation of the effects. Sham and placebo acupuncture should not be used as control groups. More positive and reliable outcomes from the administration of acupuncture can be expected if acupuncture is compared only with usual care.
Author response: According to Reviewer's comment, we have modified the eligibility criteria that we would remove sham acupuncture as a control intervention (page 8, lines 9-12). It is really true as Reviewer suggested that any types of skin stimulation including minimal, superficial penetrating, or

touches using a blunt tip would cause central and peripheral responses, and according to TCM theory, stimulation to non-traditional acupoints can also trigger responses involving the functions of the cutaneous regions (pi bu). We believe that Reviewer's suggestion can contribute to a more clear interpretation of the effects. We will update this correction on the PROSPERO registry.

Reviewer 2（Dr. Guohua Lin, Guangzhou University of Chinese Medicine）

Thank you very much for pointing out our problems and making thoughtful comments.
Response to comment 1：Current acupuncture applications and research mainly focus on traditional manual acupuncture and electro-acupuncture, is there any evidence that other acupuncture methods (such as those listed by the author) may have significant effects on PHN?
Author response: It is very true as Reviewer suggested that traditional manual acupuncture and electro-acupuncture are commonly investigated in studies involving acupuncture therapies. In the management of PHN, some other types of acupuncture methods may also be helpful, for example, fire needling has been recommended in a clinical guideline launched by the WHO's Western Pacific Regional Office,1 as we mentioned in discuss section (page 13, lines 50-57). In our study, we will also include trials using moxibustion, and recent meta-analyses have presented the analgesic effect of moxibustion on PHN.2 3 Therefore, we believe that a NMA comparing different acupuncture therapies for PHN is needed and the result can help clinical practice.
1.Liu ZS, Peng WN, Liu BY, et al. Clinical practice guideline of acupuncture for herpes zoster. Chin J Integr Med 2013;19:58-67.
2.Wang Y, Shang H, Wang F, et al. Systematic Evaluation and Meta-analysis on the Therapeutic Effect and Safety of Heat-Sensitive Moxibustion in the Treatment of Postherpetic Neuralgia. Guangming J Chin Med 2021;36:675-80.
3.Wu Q, Hu H, Han D, et al. Efficacy and Safety of Moxibustion for Postherpetic Neuralgia: A Systematic Review and Meta-Analysis. Front Neurol 2021;12:676525.

Response to comment 2：The primary outcome described in this protocol is measurements of pain intensity. As a variety of measurement methods were listed in the protocol, the evaluating approach should be clear.
Author response: According to Reviewer's comment, we have modified the primary outcome part and explained the measurements of pain intensity in more details (page 8, lines 27-33). Although different measurement scales may be used in different trials, these scales generally measure pain intensity using a score on a range between no pain to maximum pain, with higher number indicating more severe pain. Thus, continuous data for pain intensity will be presented, and MD (or SMD when different scales are used) of change score will be calculated as measure of relative treatment effects, as written in data synthesis part (page 11, lines 42-49). Therefore, we modified the description for primary outcome as following: "Therefore, we will select pain intensity as the main outcome of interest. Pain intensity is usually presented by a score on a range between no pain to maximum pain, with higher number indicating more severe pain, using the Visual Analogue Scale, Numerical Rating Scale, Verbal Rating Scale, Average Daily Pain Score, or other validated scales."

Response to comment 3：PRISMA flow chart is suggested to be presented in this protocol.
Author response: According to Reviewer's suggestion, we have added a PRISMA flow chart (figure 1) in this protocol.

VERSION 2 – REVIEW

REVIEWER	Giovanardi, Carlo Associazione Medici Agopuntori Bolognesi - AMAB, Acupuncture
REVIEW RETURNED	05-Jan-2022

GENERAL COMMENTS	The manuscript aims to focus on the efficacy of acupuncture therapies for pain relief, but there are two major limitations: 1) the concept of dose-acupuncture is not defined, i.e. number of sessions, number of acupoints and de qì. The authors themselves say that they have considered neither acupoint selection nor specific details of manual techniques; 2) Regarding the types of control groups, they are not clearly stated. Should sham acupuncture be included, then that would be a bias because sham acupuncture is not inert, as already widely acknowledged in the literature.

REVIEWER	Lin, Guohua Guangzhou University of Chinese Medicine
REVIEW RETURNED	14-Jan-2022

GENERAL COMMENTS	1. The article lacks a registration number; 2. The writing of the article does not follow the principle of prisma, such as: lack of flow chart. 3. The research topic of the article is not innovative, and similar research results have been published: see PMID: 33217857 for details.

VERSION 2 – AUTHOR RESPONSE

Response to comment 1: The concept of dose-acupuncture is not defined, i.e. number of sessions, number of acupoints and de qì. The authors themselves say that they have considered neither acupoint selection nor specific details of manual techniques.

Author response: According to Reviewer's comment, we have modified the additional analyses section that we plan to added a subgroup analysis with respect to the dose-acupuncture effect. According to published reviews, following parameters have been considered: (1)number of points needled during each treatment, (2)de qi response, (3)frequency of treatment, (4)number of treatment sessions.1,2 However, in the clinical practice of acupuncture for PHN, the number of needled acupoints is largely depended on the size of affected area, eg, for surround puncturing method, generally 10 to 30 needles are used.3 And for some acupuncture therapies, eg, pyonex, moxibustion, cupping/bloodletting, the number of needled points and de qi response are hard to define. Therefore, we believe that measure the dosage of acupuncture by the number of needled points and de qi response may not be applicable in this NMA. For the frequency of treatment and the number of treatment sessions, the current evidence suggests that for chronic pain, in general, 6 treatments at once a week may not be sufficient and that 2 or more treatments a week for 6 to 12 weeks would be a more reliable dose.4 Therefore, we would like to consider if a treatment frequency of at least 2 sessions per week and a total number of at least 12 sessions were applied in the treatment regimen. Thus, we added the following part in the additional analyses section (page 13, lines 7-23): "As dose of acupuncture treatment is an important factor that can influence treatment efficacy, a subgroup analysis involving different dosage of the acupuncture therapies on the main outcome will be performed. The concept of adequate acupuncture dose has been introduced in several systematic

reviews. Accordingly, we will define a 'high dosage' of acupuncture treatment when both the following criteria are met: (1) the treatment frequency is ≥2 sessions a week, and (2) the total number of treatment sessions is ≥12. When only one of (1) or (2) is met, the treatment will be defined as 'medium dosage', and when neither of them are met, the treatment will be defined as 'low dosage'."

1.Sun N, Tu JF, Lin LL, et al. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. Acupunct Med 2019;37:261-267.

2.Giovanardi CM, Cinquini M, Aguggia M, et al. Acupuncture vs. Pharmacological Prophylaxis of Migraine: A Systematic Review of Randomized Controlled Trials. Front Neurol 2020;11:576272.

3.Liu ZS, Peng WN, Liu BY, et al. Clinical practice guideline of acupuncture for herpes zoster. Chin J Integr Med 2013;19:58-67.

4.Bauer M, McDonald JL, Saunders N. Is acupuncture dose dependent? Ramifications of acupuncture treatment dose within clinical practice and trials. Integr Med Res 2020;9:21-27.

Response to comment 2: Regarding the types of control groups, they are not clearly stated. Should sham acupuncture be included, then that would be a bias because sham acupuncture is not inert, as already widely acknowledged in the literature.

Author response: According to Reviewer's comment, we have clarified that our study will not included sham acupuncture. It is really true as Reviewer suggested that sham acupuncture is widely considered not inert, and we agree that comparing sham acupuncture with various acupuncture therapies will confuse rather than clarify the interpretation of the treatment effects. Therefore we add the following part in types of control groups part (page 8, lines 15-20): "We will also exclude studies using sham acupuncture in the control groups, as sham acupuncture is widely considered not inert, which may cause confusion when compare with various types of acupuncture therapies."

Reviewer 2 (Dr. Guohua Lin, Guangzhou University of Chinese Medicine)

Thank you very much for pointing out our problems, your comments help us a lot to improve this manuscript.

Response to comment 1: The article lacks a registration number.

Author response: This study protocol had been registered on PROSPERO. We had provided the registration number (CRD42020219576) in Abstract (page 3, lines 44-45). According to reviewer's comment, we now also add this number in the Method section (page 7, lines 26-27).

Response to comment 2: The writing of the article does not follow the principle of prisma, such as: lack of flow chart.

Author response: The initial submission of this study protocol were lack of PRISMA flow chart, and according to Reviewer's suggestion, we added a PRISMA flow chart in last revision, as we presented in figure 1 (page 23, lines 6-41).

Response to comment 3: The research topic of the article is not innovative, and similar research results have been published: see PMID: 33217857 for details.

Author response: According to Reviewer's comment, we have partially revised the discussion section (page 14, lines 11-37). It is true as the Reviewer believed that with the increasing publication of clinical studies on acupuncture and related therapies for PHN, many researchers have investigated efficacy of acupuncture treatment for PHN using the SR/MA method. Article PMID: 33217857 is a study protocol of an overview of SRs/MAs, authors of that study plan to combine the reviews of acupuncture therapy for treating PHN in a narrative summary, appraise the quality of these reviews and discuss the optimized acupuncture therapy based on included pairs of comparisons. However, our study will compare the effect of different acupuncture therapies on PHN using the NMA method, as NMA method is intrinsically suitable for comparing the effects of multiple interventions simultaneously. And in existing MAs, the data of integrated use of two or more acupuncture therapies were not included or directly pooled with the use of single acupuncture therapy, which may cause confusion for the interpretation of the results.1,2 Our NMA will clearly define the types of included acupuncture and their integrated use, as we stated in types of intervention part (page 7, lines 50-59). In addition, within the Bayesian framework, we plan to perform a network meta-regression to examine the influence of potential effect modifiers and subgroup analysis with respect to treatment frequency and number of treatment sessions. To best of our knowledge, there's no published research result of comparing the efficacy of various acupuncture therapies for PHN using the NMA method. Therefore, we believe that our study is necessary and the result will provide credible evidence of acupuncture therapy for PHN.

1.Wu Q, Hu H, Han D, et al. Efficacy and Safety of Moxibustion for Postherpetic Neuralgia: A Systematic Review and Meta-Analysis. Front Neurol 2021;12:676525.

2.Wang Y, Shang H, Wang F, et al. Systematic Evaluation and Meta-analysis on the Therapeutic Effect and Safety of Heat-Sensitive Moxibustion in the Treatment of Postherpetic Neuralgia. Guangming J Chin Med 2021;36:675-80.