PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Acupuncture for Insomnia with Short Sleep Duration: Protocol for a Randomized Controlled Trial
AUTHORS	Wang, Cong; Yang, Wen-jia; Yu, Xin-tong; Fu, Cong; Li, Jin-jin; Wang, Jing; Xu, Wen-lin; Zheng, Yi-xin; Chen, Yun-fei

VERSION 1 – REVIEW

REVIEWER	Eric Zhou Harvard Medical School, USA
REVIEW RETURNED	26-Aug-2019

GENERAL COMMENTS	This manuscript nicely describes the planned study protocol. If this type of work is within the purview of BMJ Open, then should the authors address the points below, it is done well enough to warrant publication. Overall, some phrases are not presented well, such as “patients who are accompanied by short sleep duration” should be “patients with short sleep duration.” Introduction - It is not appropriate to refer to authors in citations by their first name and middle initial (“Christina J and her team”). - Please elaborate on why CBT-I may be less effective among those with short sleep duration. It does not lack ‘specificity for the treatment of insomnia with objective short sleep duration.” It is also entirely not true that “these patients can only resort to sleep medicine.” - Please provide a citation demonstrating that “many people with insomnia seek complementary and alternative medicine, such as acupuncture.” - Substantially more real estate in the Introduction should be dedicated to the hypothesized or proven mechanisms by which acupuncture may improve insomnia in someone with short sleep duration, and to describe different acupoints that are used for the treatment of insomnia. This is the entire focus on this manuscript, yet there is nothing other than a few self-citations loosely capturing this. Methods - Why was the PSQI used as the primary study outcome measure (and thus, used for sample size calculations)? - How was the ‘dose’ of acupuncture determined? The follow up period is 8 weeks, but not clear why. - What actigraph will be used? What scoring algorithm will be used? - Why is a baseline PSG conducted, when there is no follow-up?

	- How will a history of acupuncture treatment be assessed? - Will participants who complete the actigraphy, before group assignment, but then drop out of the study, be compensated for their efforts?

REVIEWER	Simon Hayhoe Colchester University Hospital, UK
REVIEW RETURNED	06-Sep-2019

GENERAL COMMENTS	This is a well planned protocol to investigate the use of acupuncture in a sub-group of insomnia. 1. In “Method” under “Outcome measures” there is excellent explanation of both primary and secondary data to be collected, but under “Interventions” there has been no explanation of the Streitberger needle to be used for the control group. Previous researchers have reported some specific problems which will need to have been addressed before starting the trial. First, since the needles will be in place for 20min they will need to be firmly affixed to the skin or scalp. This is not easy, as the supplied attachment has often been found inadequate. Others have used tape or hair clips for stabilisation. How do you intend to keep these needles in place, particularly at points on the crown of the head within the hair? Second, even acupuncture naive subjects question why the needle is strangely packaged. How are you going to explain this? Third, although the skin is not pierced, depression of the blunt needle causes a pricking sensation. This is akin to a form of acupressure, and some have claimed it is therefore not a placebo, but a physiologically active application. This needs to be mentioned in your discussion. 2. In “Method” under “Inclusion criteria”, item (4): do all the four of PSQI, ISI, BAI, and BDI need to be within the required parameters, or only some? 3. Under “Secondary outcome measures” third paragraph (BAI) a sentence has slipped in stating “This study will exclude subjects with non-primary insomnia.” This is not mentioned in the lists of inclusion or exclusion criteria (or indeed elsewhere) although certainly many major diseases are excluded. Very common causes of secondary insomnia are arthritis and prostatic hypertrophy both of which might respond to more complaint directed acupuncture, with consequent reduction in insomnia. I presume it is intended to be stated that all causes of secondary insomnia are excluded and that primary insomnia should be a requirement for inclusion? If it is indeed intended to be primary insomnia only, then this should be specified in the Abstract and Study design. 4. Subjects sign an informed consent form, but what are they told? Are they told that one group will have placebo acupuncture, or that two forms of possibly active treatment will be used? It would be useful to ask subjects if they believe they are receiving active treatment. This should be recorded in table1. Subjects are put to significant inconvenience to take part in this trial, so will they be offered an active treatment at the end of the trial if they had been in the control group? 5. Drop-outs and Compliance are to be recorded in table 1, but how are these handled for statistical purposes? What happens to withdrawals after randomisation (intention to treat)? How are missing data dealt with?

VERSION 1 – AUTHOR RESPONSE

reply to Reviewer: 1
The reference method has been modified.
Introduction has been modified as required.
Methods:
-Because PSQI and ISI can evaluate global sleep and insomnia symptoms, many guidelines recommend both as an essential indicator for measuring and reporting about insomnia symptoms [28] [52]. And PSQI was verified as a reliable and valid measure of subjective sleep quality in clinical practice and experimental research [53-54]. At the same time, combined with our previous research results, the primary outcome of this study will be the changes in the PSQI and ISI between the baseline, post-treatment assessment, one-week follow-up and one-month follow-up (Table 1). And PSQI will be used for sample size calculations.
-And subjects in both groups will be treated three times per week for 10 times by the same acupuncturist.The follow up period is 8 weeks,Because we are based on previous research, this study mainly observes the short-term efficacy of acupuncture for insomnia.
-The motion watch 8 wrist ACT produced by CamNtech Ltd will be used in this study.The recorded sleep and activity data will be analysed by the corresponding MotionWare Software.Changes in the number of awakenings (NOA), total wake time (TWT), total sleep time (TST), and sleep efficiency (SE) will be measured before and after treatment.
-PSG (NIHON KOHDEN, Japan) in this study will be used for screening purposes only.
-We will use a self-made scale to evaluate a history of acupuncture.
-They will also get compensation. Our compensation measures include an additional 10 acupuncture treatments and transportation subsidies.

reply to Reviewer: 2
1.Since the Streitberger needles will be in place for 20min, they will need to be firmly affixed to the skin or scalp. We have modified the procedure by using surgical tape (or hairpins in hairy regions) to hold the needles in place. This enables the needles to be applied in hairy regions and different needling directions to be attempted. Such a method has been adopted by mang other researchers [50].
Firstly, each patient will be treated in a separate bed, opaque curtains separated in the middle. Secondly,They will be informed about the acupuncture as follows: “In this study, different types of acupuncture treatment will be compared. One type is the usual acupuncture, and the other is associated with positive outcomes in previous clinical studies.”
Already explained in the discussion： The use of placebo control in acupuncture trials remains controversial [80]. In pharmacological treatment trials, an ideal placebo should be indistinguishable from the true interventions and be physiologically inert [81]. However, it remains a challenge to design an adequate placebo for non-pharmacological interventions, such as acupuncture, in which non-specific treatment will be exists in the placebo group [82]. Since placebo acupuncture can produce a significant non-specific therapeutic effects, there is little space left for the assumed specific effect of acupuncture [83]. Therefore, we expect that in the future research work, researchers will invent a more authoritative placebo acupuncture.
2.need to be meet all the required parameter.
3.Our name of "non-primary insomnia" is wrong here. We use the diagnostic criteria for chronic insomnia in ICSD-3, the classification of primary insomnia and secondary insomnia is no longer used in this guide. We just include chronic insomnia rather than primary insomnia.So we corrected the statement here.
4.They will be informed about the acupuncture as follows: “In this study, different types of acupuncture treatment will be compared. One type is the usual acupuncture, and the other is associated with positive outcomes in previous clinical studies.” The success of subject-blinding will be assessed by, at the end of the last treatment session, asking the subject if they believe they are

receiving active treatment(table1).
Our compensation measures include an additional 10 acupuncture treatments and transportation subsidies.
5.Subjects may withdraw from the study at any time for any reason. If any subject wishes to withdraw, the clinician will ask if they are willing to complete the final assessment and record the time of the last treatment. The incidence of withdrawal and loss to follow-up will be recorded and reported. We will also inquire the subjects about the reasons for absence, and will record compliance by the clinician. Participants who withdraw after randomisation but priorto receiving the intervention are also defined as dropouts. Data from dropout cases will be managed by both per-protocol (PP) analysis and intention-to-treat (ITT) analysis to evaluate the influence of missing data.
The multiple imputation method will be the primary method for processing the missing data, and an observation carried forward method will also apply to sensitivity analysis [73]. Data from dropout cases will be managed by both ITT analysis and PP analysis.

VERSION 2 – REVIEW

REVIEWER	Eric Zhou USA
REVIEW RETURNED	08-Oct-2019

GENERAL COMMENTS	There are issues that persist, that are not adequately addressed by the authors. Introduction - The response explaining why CBT-I may be less effective among those with short sleep duration does not adequately explain the issue. I do not understand what the authors mean by “It’s different from the pathological mechanism of this phenotype.” - The citation referenced does not provide any data suggesting that “many people with insomnia seek complementary and alternative medicine, such as acupuncture.” It is a review of the literature of RCTs, not of community/public interest in treatment. - The authors do not separate hypothesized vs proven mechanisms by which acupuncture may improve insomnia in someone with short sleep duration. The use of phrases such as “and so no” does not demonstrate an understanding of the issue. Methods - The PSQI is not recommended as an “indicator for measuring and reporting about insomnia symptoms.” It is designed as an assessment tool for sleep quality, and potentially captures the impact of other sleep disorders. - The authors do not provide an explanation for how the ‘dose’ of acupuncture was determined. - The authors still did not report on the scoring algorithm used for actigraphy data. - The authors still do not explain why a baseline PSG conducted, when there is no follow-up. What were they screening for? - The authors say they “will use a self-made scale to evaluate a history of acupuncture” but fail to provide data on the development of this scale and whether it has any external validity.

REVIEWER	Simon Hayhoe Essex Partnership University Trust, UK
REVIEW RETURNED	07-Oct-2019

GENERAL COMMENTS	Thank you: my questions and suggestions have now been effectively addressed. Best wishes for a successful trial.

VERSION 2 – AUTHOR RESPONSE

Reply to Reviewer 1
-Thanks to the reviewer for providing such meticulous review comments. After this revision, our articles have been greatly improved. The reviewer was so meticulous and careful that we were sorry that we did not understand the meaning of the reviewer during the first revision.

Introduction
- The response explaining why CBT-I may be less effective among those with short sleep duration does not adequately explain the issue. I do not understand what the authors mean by "It's different from the pathological mechanism of this phenotype."
The short objective sleep duration phenotype has a dull response to CBT-I because of behaviourally based approach aimed at decreasing cognitive–emotional arousal, altering unhealthy sleep-related behaviours and beliefs and changing sleep misperceptions [15]. However, the short objective sleep duration phenotype is mainly associated with cortical, and physiological hyperarousal (i.e., short sleep duration and activation of the stress system), and non-remitting course [10]. Obviously, CBT-I does not completely solve the symptoms of this phenotype. But it will respond better to treatments that primarily aim at decreasing physiological hyperarousal (e.g., cortisol) and increasing sleep duration, such as medication or other biological treatments [16].

- The citation referenced does not provide any data suggesting that "many people with insomnia seek complementary and alternative medicine, such as acupuncture." It is a review of the literature of RCTs, not of community/public interest in treatment.
Therefore, many people with insomnia seek complementary and alternative medicine, such as acupuncture, especially in China [19].
[19] China Sleep Research Association. Guidelines for the diagnosis and treatment of insomnia in China. National Medical Journal of China. 2017; 97(24): 1844-1856.

- The authors do not separate hypothesized vs proven mechanisms by which acupuncture may improve insomnia in someone with short sleep duration. The use of phrases such as "and so no" does not demonstrate an understanding of the issue.
We hypothesized that individuals with insomnia and short sleep duration, would have a better treatment response to acupuncture than individuals with insomnia and normal sleep duration. We made this prediction because some studies have found that insomnia with objective short sleep duration is associated with activation of the stress system, especially the activation of the HPA axis, and the group with an objective short sleep duration had a higher amount of cortisol (COR) compared to the group with normal sleep duration [16] [24-25]. Previous studies about acupuncture have shown that acupuncture can regulate the activity of the HPA axis and reduce adrenocorticotropic hormone (ACTH), corticotrophin releasing hormone (CRH) and COR levels in peripheral blood [26-27]. According to the theory of TCM, the main causes of insomnia are Yin deficiency leading to excessive fire, incoordination between the heart and the kidney, disturbance of heart due to phlegm heat, deficiency of both heart and spleen and liver depression forming fire [28]. Therefore, we chose acupoints based on disease differentiation and special acupoints combinations to nourish Yin and drain fire, calm the mind and regulate mentality. SP 6 (Sanyinjiao) and HT 7 (Shenmen) are adopted as the main points to nourish Yin and drain fire, especially used to nourish liver and kidney Yin and decrease heart fire [29]. PC 6 (Neiguan) is the collateral point of the hand-jueyin pericardium meridian, which is also specific acupuncture point of the eight confluent points. It's used to cool pericardium and restore consciousness [30]. We also use GV20 (Baihui) and Ex-HN 1 (Sishencong)

to make the brain-activating and mind-tranquilizing [31].

Methods
- The PSQI is not recommended as an “indicator for measuring and reporting about insomnia symptoms.” It is designed as an assessment tool for sleep quality, and potentially captures the impact of other sleep disorders.
- We agree with the reviewer that the PSQI is not suitable as an indicator for measuring and reporting about insomnia symptoms because it potentially captures the impact of other sleep disorders. We still use it as the primary study outcome measure and used for sample size calculations, mainly considering that we have already excluded potential subjects with other sleep disorders through outpatient interviews and PSG at the baseline. The selected subjects will be simple chronic insomnia patients. And some previous studies [1] [2] have also used PSQI as the primary study outcome measure and used for sample size calculations.
[1] Fu C, Zhao N, Liu Z. Acupuncture Improves Peri-menopausal Insomnia: A Randomized Controlled Trial. Sleep. 2017;40(11). doi: 10.1093/sleep/zsx153.
[2] Guo J, Huang W, Tang CY, et al. Effect of acupuncture on sleep quality and hyperarousal state in patients with primary insomnia: study protocol for a randomised controlled trial. BMJ Open. 2016;6(3): e009594.

- The authors do not provide an explanation for how the ‘dose’ of acupuncture was determined.
- Subjects in both groups will be treated three times per week for 10 times by the same acupuncturist. As the subjects will come to the hospital for acupuncture, the thrice-weekly treatment schedule, but not a more frequent treatment, was selected to enhance treatment adherence, and the 10 times treatment duration was chosen to examine the short-term effect of acupuncture. Our previous research [1] and other studies [2] [3] have adopted the similar approach, this ‘dose’ of acupuncture has been proven to achieve good efficacy and good compliance through by previous research [1].
[1] Fu C, Zhao N, Liu Z. Acupuncture Improves Peri-menopausal Insomnia: A Randomized Controlled Trial. Sleep. 2017;40(11). doi: 10.1093/sleep/zsx153.
[2] Chung KF, Yeung WF, Yu BY, et al. Acupuncture with or without combined auricular acupuncture for insomnia: a randomised, waitlist-controlled trial. Acupunct Med. 2018;36(1):2-13.
[3] Yin X, Gou M, Xu J, et al. Efficacy and safety of acupuncture treatment on primary insomnia: a randomized controlled trial. Sleep Med. 2017;37:193-200.

- The authors still did not report on the scoring algorithm used for actigraphy data.
- Changes in the number of awakenings (NOA), total wake time (TWT), total sleep time (TST), and sleep efficiency (SE) will be measured before and after treatment. NOA: The number of parts of the sleep stage classified as "awakening". TWT: The total time spent in awakening from turning off the light to getting up. TST: Total time spent sleeping from turning off the light to getting up. SE: Total sleep time as a percentage of total time in bed. All data are averaged value over the seven days of the data from ACT. And linear mixed models will be used to analyze the effects of the acupuncture or placebo intervention on ACT measures of NOA, TWT, TST, and SE before and after treatment.

- The authors still do not explain why a baseline PSG conducted, when there is no follow-up. What were they screening for?
- PSG (NIHON KOHDEN, Japan) in this study will be used for screening purposes only. It will use to exclude potential participants with obstructive sleep apnea or restless legs syndrome. We will use the following exclusion criteria: An apnoea–hypopnea index (AHI) >10 or periodic limb movements index during sleep associated with >15 arousals per hour on diagnostic PSG.

- The authors say they “will use a self-made scale to evaluate a history of acupuncture” but fail to provide data on the development of this scale and whether it has any external validity.
- The reviewer ponders the issue quite carefully, the scale is just a self-made and has no external

validity. The purpose of our self-made gauges is simply to remind the researcher not to miss some questions. It's just a list of simple questions about how to do the clinic visit, such as " Have you ever had acupuncture treatment before?" "Do you know the meaning of Deqi?" "Can you describe the feeling of Deqi?" and so on. It is just a written form of clinical interviews. In addition, we will also check the patient's electronic medical record to see if there is a history of acupuncture.