Author's response to reviews

Title: Effects of acupuncture treatment on depression insomnia: A study protocol of a multi-centre randomized controlled trial

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Effects of acupuncture treatment on depression insomnia: 
A study protocol of a multi-centre randomized controlled trial

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Abstract:

Background: 
Insomnia is one of the main symptoms harassing patients with depression. More than 70% of those patients, who come to visit the doctors, are with sleep disorder. The treatment for insomnia is a very important link for depression treatment. Meanwhile, the anti-depression treatment is also important for this kind of insomnia. When it comes to acupuncture treatment, we are using Lu-7 ( Lie Que) and Kid-6 (Zhao Hai ), which are two of the eight confluence points, as the main points and subcutaneous needles at Bl-15 (Xin Shu) and Bl-23 (Shen Shu), or Bl-19 (Dan Shu), and N-HN-54 (An Mian) points to consolidate the treatment solutions. Its adequate curing effect is well proved in the practice by our senior acupuncturists in Guangdong Provincial Hospital of Traditional Chinese Medicine (TCM). Therefore, we have designed a set of optimized acupuncture treatment formula here and would like to examine if this set of optimized clinical formula is able to increase the clinical efficacy of insomnia caused by depression.

Method/Design

Randomized controlled multi-centre trial, will be applied in this trial with patients diagnosed with depression insomnia. All the eligible participants, aged from 16 years to 50 years, both male and female, will be randomly assigned to receive either normal acupuncture treatment or optimized acupuncture treatment. Normal acupuncture treatment will be applied as the control group, and optimized acupuncture
treatment will be applied as the treatment group. Duration of the study: Approximately 36 months.

**Discussion**
The trial will utilize high quality of trial methodologies which may provide better evidence for the effectiveness of acupuncture as a treatment for depression insomnia. Trial will be conducted in accordance with protocol and in compliance with the moral, ethical and scientific principles governing clinical research as set out in the declaration of Guangdong Provincial Hospital of TCM. General acupuncture department and scientific research department of Guangdong Provincial hospital of TCM, along with each branch research center, are responsible for designing and conducting of the trial, including randomization and documentation of patients’ data. Data management and statistical analysis including randomization will be performed under the guidance of DME professionals in Guangzhou University of TCM. Since the optimized acupuncture formula has potential benefits to increase the efficacy of treating depression insomnia, we would like to publish the result and the conclusion later.

**Trial registration**
The trial is registered in China (ChiCR-TRC-00000481) on August 12th 2009.

**Background**
More than 20% of Chinese suffer from depressive symptoms according to the report of World Health Organization and health minister of China. Those symptoms exist in depression and depressive neurosis. [1] Depression is a mental disorder, with various characteristic such as, negative emotions, anxiety, agitation, low-self-esteem, physical dysfunctions, dizziness and suicide etc. [2] Levels of disturbed sleep among patients, as one of the core symptoms are known to be related with depression. [3, 4] The prevalence of patients with depression and insomnia varies from 70.0%~84.7%. The insomnia symptom is likely to increase the risk of the deterioration and recurrence of depression, heart disease, social function defects and suicide rate. Also it will lower the life quality of the depression patients. [5, 6] Meanwhile, insomnia is one of the most diagnostic symptoms of depression and can be the risk factor of the intractable depression and predictor of depression disorder recovery. [7] Therefore, for those patients with depression insomnia, it cannot simply use pharmacological treatment or other therapies for the insomnia or depression. Treatment should give attention to both.

Acupuncture, as the typical Traditional Chinese Medicine (TCM) technique, has been applied for thousands of years. [8] The rapid development of acupuncture both within and outside China over the last few decades has itself led to great innovation in practice. Many studies, including clinical reports and systemic reviews, investigated the benefits and success of acupuncture in relieving symptoms for various acute and chronic diseases and plenty of clinical practice and studies show that acupuncture
appears irreplaceable effect on treating depression and its symptoms, when compared with modern medicine and its anti-depressant treatment. However, methodological difficulties have been existing. [9, 10, 11] For example, two systematic reviews by Smith in the Cochrane Collaboration show that the clinical evidences for acupuncture treatment of depression are relatively low before 2003 and the quality of the clinical trials between 2003 and 2008 have been improved. The problem of disunity of inclusion criteria and large heterogeneity existed and curative effects of the acupuncture for depression were impossible to confirm. [12, 13]

In view of these data, in this protocol, we designed this randomized controlled multi-centre study of depression insomnia patients, in the hope of determining the effectiveness of traditional acupuncture techniques. One is normal acupuncture treatment formula, and another one is optimized acupuncture treatment formula. The normal acupuncture treatment is basic one with a point–selection algorithm established on the basis of the particular TCM pattern of depression. Depression in Chinese medicine is mainly due to Liver Qi block, giving rise to the symptoms appears to be mental disturbance. Meanwhile, filiform needle therapy is applied. The optimized group is the modified one. The empirical points were added on the basis of the normal one and filiform needle therapy is applied on the other. Meanwhile, subcutaneous needle therapy has proved to be effective for chronic disease or for those diseases demanding for longer retaining time. Two groups of points are selected to coordinate with therapy. [14]

Besides, measurement system for evaluating the progression of the illness was used to compare the exact effect of different acupuncture treatment formula.

**Method/Design:**

**Trial objective**

The objective of this trial is to evaluate the effectiveness of treating depression insomnia by either normal acupuncture treatment scheme or optimized acupuncture treatment scheme.

**Hypothesis**

Acupuncture is capable of reducing the levels of depression, whether in normal treatment scheme or optimized treatment scheme. Furthermore, optimized acupuncture is capable of reducing the levels of depression insomnia, to a greater degree than is normal acupuncture. Meanwhile, the scientific evaluation results from the application of those optimized formula of acupuncture treatment for depression insomnia are supposed to gain, in the hope of increasing the clinical efficacy of depression, improving the health-related life quality of depression patients, and moderating the consumption of drugs used in conventional treatment, and finally making significantly social and economic benefits.

**Design**

Controlled multi-centre prospective study, with random assignation, to receive
optimized acupuncture (treatment group), or normal acupuncture (control group) with a 1:1 allocation ratio. (Figure1) Patients will be stratified and will be blinded to both types of the treatment. The evaluation of patients and analysis of results will be performed by professional blinded to the assignation of treatment options.

**Eligibility**

**Inclusion criteria**
1. Meet the 3rd edition of the Chinese classification and diagnostic criteria of mental disorder (CCMD-3) diagnostic criteria for depression;
2. With insomnia for the No.1 chief compliant;
3. HAMP count should be more than 20 points but less than or equivalent to 35 points;
4. The total PSQI count should be more than or equal to 7 points;
5. Conscious patients without aphasia and mental retardation and with primary education who can understand the content of scale and be in line with treatment;
6. Age from 16 years to 50 years, male or female;
7. The course of disease is between 2 weeks and 2 years.

**Exclusion criteria**
1. Except depression which is caused by organic mental retardation, or psychoactive and non-addictive substances;
2. Age less than 18 years or more than 65 years;
3. Patients who can not understand the content of scales and carry out efficacy evaluation;
4. Pregnant women, patients with cardio-cerebral blood vessels, liver, kidney, and hematopoietic system diseases, and those who fear acupuncture;
5. Those who can not be in line with the treatment arrangements.

**Subject withdrawal criteria and the management**

Subject withdrawal or drop-out criteria
1. At the participants’ own request or at the legal representative;
2. The participants who have the outbreak of serious disease such as heart disease, pneumonia and other diseases, and in the investigator’s opinion, they are not suitable to keep taking part in the research;
3. If, in the investigators’ opinion, the compliance of the participant is poor, and suitable to keep taking part in the research;
4. The participants have the adverse reaction related with acupuncture treatment; the investigator is not suitable for the research.

**The management for those withdrawn subjects or drop-outs**
1. The withdrawn patients should be documented in the “clinical trial performance forms” in case report file (CRF) of the patients;
2. The withdrawn patients due to adverse events or reaction should be documented in “adverse events/reaction record forms” in CRF;
3. If the subjects have been determined as drop out or withdrawn cases and patients require continuing the treatment, the investigators should provide treatments, however, the patient should not be documented as subjects.

All the withdrawn patients will report in the final results to guarantee maximum transparency.

Setting and participants
The study protocol was designed according to the Standards for Reporting Interventions in Clinical Trials Acupuncture (STRICTA) [15]

Sample Size
Unfortunately, there have been few clinical trial reports of acupuncture treatment for depression insomnia according to the review of the previous literature. Based on our rich clinical experience of senior acupuncturists in Guangdong Provincial Hospital of TCM. [16, 17] We believe that the successful cure rate for depression insomnia is approximately 40% when adopting the normal acupuncture formula to depression and an increase of success rate by 30% or more to >=70% in the optimized acupuncture formula would be clinically relevant and therefore could impact clinical practice. A sample size of n=58 evaluable patients per group is necessary (PEMS v3.1 software package). The drop-out rate within the intervention is expected to be about 15%. Therefore, another 24 patients in total have to be randomized to obtain the required number of evaluable patients. The total number of patients needed to be randomized is therefore 140.

Recruitment of patients
The patients are referred by the doctors and acupuncturists from each branch centers in Guangzhou, Huizhou, and Zhaoqing city. 70 patients are from Guangdong Provincial Hospital of TCM. 35 patients are from the second people’s hospital of Zhaoqing city and another 35 patients are from people’s hospital of Huizhou city. The anticipated data of the first enrolment is 2009-08. The anticipated data for the last enrolment is supposed to be 2011-08.

Randomizations and procedures for setting.
The study procedures, risks, benefits and data management will be clarified in detail before the patients are asked to give their informed consent. The eligible participants are divided into two groups, one group is control group (indicate as 1 in CRF) and another group (indicate as 2 in CRF) is treatment group. These groups all adopt the acupuncture prescription as basic treatment and the treatment group will add the acupuncture points and techniques especially for insomnia. The proportion will be in accordance with 1:1. To achieve comparable groups for known and unknown risk factors, randomization will be performed as a simple randomization. After inputting the estimated sample size into PEMS v3.1, sequence number, seed number, center
number and result of the allocation will be gained. And then the allocation to the treatment group will be performed by sealed consecutively numbered envelopes prepared by the trial team. Since this is a multi-centre trial, after the patient is registered, the practitioners will be informed, by telephone or by other instant messengers, of the patient’s assignation to one of the two study schemes. The procedure ensures that the randomization is not influenced by the investigators taking part in this study. The practitioner participating in the study will not take part in the randomization process.

**Study Treatment**

The patients taking part in the study will each receive 24 acupuncture sessions (twice per week), either normal or optimized, as follows:

The treatment will be performed after sterilizing the skin on the areas and with patients lying face up. The temperature of the treatment room is not lower than 25°C.

**a) Normal acupuncture**

All the patients in the intervention group 1, as the control group, will receive the normal acupuncture formula at the following points: Si Guan (LI4, LIV3), Yin Tang (Ex-HN3), and Bai Hui (GV20). The needles we are applying, are produced by Su Zhou Tian Xie acupuncture limited company. The size is 0.35*25mm. The needle will be maintained in the points for 30 minutes. During the treatment, after the De Qi sensation, patients are required to breathe deeply for 6 times and then have rest, followed by another 6 times every minute till taking out the needles.

**b) Optimized acupuncture**

The basic treatment scheme is modified. On the basis of the normal acupuncture, Lu-7 (Lie Que) and Kid-6(Zhao Hai) are added and needle will remain in the body after patient feel the De Qi sensation. And then subcutaneous needles are buried, and the points will be carried out for two groups of points (1) Bl-15 (Xin Shu), Bl-23(Shen Shu), and Bl-19 (Dan Shu), N-HN-54 (An Mian), those two groups of points are used alternatively. The subcutaneous needle of granular type is used, and the length of the needle tip is about 2-3mm. Clamp the needle loop with forceps and insert the needle underneath the skin perpendicularly and fix it with 3M medical proof fabric and take it off before the next treatment.

In order to minimize the treatment bias, all the practitioners and acupuncturists who participate in this trial are well-trained acupuncturists of general acupuncture department and each research centre. All of them gained medical license of China and were well-trained according to the trial’s procedure under the guidance of senior acupuncturists.
Common acupuncture adverse events/reaction and processing

(1) Common acupuncture adverse events/reaction

1. Needle fainting during the acupuncture treatment
For patients who are on the first visit or who have a serious phobia about the needles, a reassuring explanation of what to expect in acupuncture will be given and the complexion of patients will be closely observed to check if there is any early symptoms of needle fainting, such as discomfort, dizziness, pale face, tiredness, sudden cold sweat, cold limbs, weak breathing, pale and green complexion, blue lips, low blood pressure, and obnubilation. Once the symptoms occur, needles should be taken out as soon as possible. Keep the patients horizontal with the feet slightly raised and offer them warm sugar water. If the symptoms are serious, Du-26 (Shui Gou), Du-25 (Su Liao), Pc-6 (Nei Guan), and St-36(Zu San Li) points are selected as emergency points. If the symptoms persist, other professional emergency measures may need to take.

2. Convulsions
To all the participants, whether they have a history of seizures must be questioned. To those who have convulsion history during the acupuncture treatment, close observation are needed. Once the convulsions occur, the practitioner will remove all the needles and take some emergency measures. If the disease is not immediately controlled or the convulsions persist, the participants need to be transferred to emergency centre immediately.

3. Severe pains
(1). During the process of the insertion, the severe pain is usually caused by the practitioners’ unskilled methods for inserting the needle, the blunt tip of the needle, belt hooks or the thick body of the needle, or sometimes, the pain occurred only because the patient is hypersensitive.
(2). After the insertion of the needle, the reason of severe pain is that the needle tip touches the pain receptor of the nerve fiber. If this kind of condition occurs, the needles are expected to take underneath the skin and then we are going to change the direction of the needle and insert the needle again. The pain occurred during the retaining of the pain is due to the change of the patients’ position, and will be relieved when getting back to correct position.
(3). Pain after the treatment is usually caused by improper needle manipulation, or too strong stimulation. When the pain is gent, local compress is used to stop the pain. When the pain is heavier, moxa can be applied, in addition to local compress.

4. Needle sticking
After inserting the needles, the practitioner may feel the difficult sense of rotating, lifting, thrusting, and taking the needles out or unable to conducting those processes. The reason for the sticking of needles is mainly due to the muscle contraction. A large margin of rotating needle or rotating the needle with one direction is likely to cause muscle tissue wind. Once the sticking of the needle occurs, the patients will be required to relax. If the sticking of the needle is caused by twisting the needle with one direction and the way solving the problem is rotating the needle on the opposite
If the sticking of the needles is caused by the over-contraction of the muscle, the way to deal with the problem is taking out the needle and pressing the local area of points where the needle is stuck or putting another needle in the local area in order to distract the patients’ attention. If the situation occurred due to the change of the patients’ position, it will be then relieved when they getting back to the correct position.

5. Broken needles
The main reason cause the broken needle is due to the poor quality of the needles. The needle body and handle were damaged and then the muscle contraction occurs. If the broken part of the needle body appears outside the patients’ skin, needle can be taken out the tweezers. Once the needle is broken, ask the patients to be peaceful and keep still, in case that the broken needle is sinking underneath the skin. If the broken-off part of the needle appeared outside of the body, the needle can be taken out by the tweezers.

6. Local infections
When the strict aseptic operation is ignored, the local infection occurred. Once the infection is found out, proper treatment will be needed or drug therapy is suggested.

7. Subcutaneous hematoma
During the acupuncture treatment, swelling and bruise may occur when subcutaneous tiny vessels is broken. The positive way of dealing with the problem, is using ice to stop the bleeding and applying local press and at the late stage, hot compress has been applied and herbs are used to promote blood circulation and removing the blood stasis.

(2) The assessment of the cause of effect of adverse events/reaction
If other adverse events/reaction occurs during the study process, which has not been listed above the “common adverse events/reaction”, the investigator should analyze the situation as the following aspects, in order to judge the relationship between those adverse events/reactions and acupuncture.

(1) The temporal relationship between the acupuncture and whether there is response relation.
(2) Whether the adverse events/reaction is relieved when stopping the treatment.
(3) Whether adverse events/reactions occurs again, when repeating the acupuncture treatment on condition of ensuring the security and patient’s consent.
(4) Whether the adverse events/reactions can be explained by the patients’ disease progress, new occurred disease, or other therapies the patients applied by themselves.

(3) The report for the adverse events
If the investigators find out that patients have the adverse events/reaction, it should be documented in the adverse events/reaction form in the CRF, and then the investigator is supposed to give enough comforts and treatments to the patients, in the hope of relieving the symptoms. The adverse events will be reported to the principal investigator in Guangdong Provincial hospital.
Data collection

Outcomes

(1) Primary outcomes:
The Pittsburgh sleep quality index (PSQI) and Hamilton rating scale for depression (HAMD) were applied as primary outcome for effectiveness evaluation. Changes in sleep quality, measured on scale, the construction validity and reliability of this scale have been proven in previous studies and it has been validated for use in China \[18\]. Changes in levels of depression, measured on the Hamilton hetero-evaluation scale. This scale is of proven discriminant validity, reliability, and sensitivity to change; moreover, it has been validated for use in China as well. \[19\]

(2) Secondary outcomes

--The combined medication record. Drugs such as anti-depressant, hypnotics medication consumed (whether or not prescribed by the patient’s doctor) during the trial will be recorded and measured on a special scale.
--Blind method cognitive evaluation
--Baseline variables of patients such as age, sex, education level, profession, income level, weight (kg) and height (cm).
--Side effects and adverse reactions. A record will be made of the side effects and possible adverse reactions arising from the treatment.

Extramural judgment will be applied when it comes to curative effect evaluation. The data required for evaluating the effectiveness of the treatment will be collected at baseline, at the start of the treatment, 1 month after the treatment has begun, 2 month after the treatment has begun, and at the end of the treatment. The data required for the blind method cognitive evaluation will be collected after the 2\textsuperscript{nd} acupuncture treatment, and the last treatment.

Data storage and confidentiality

The data compilation form containing the variables of interest and this will be completed by the corresponding researcher at each center. Data will be documented in the paper CRF by researchers or evaluators and will be double checked by the quality inspectors. The supervisor will inspect the progress of the trial at regular intervals in each branch centre, and check the CRF and contact some of the participants to verify the materials. All the detailed original data (paper CRF) will be recorded timely, clearly, and completely. And the case reports will then be modified only by researchers who are documenting the data. The correct way of modification is making a lineation on the original data and taking down the revised data next to the original data. The modified data will be documented with data and abbreviation name of the investigator who are doing the medication. All the materials will be kept for 5 years after the completion of the study exercise. At each centre, the information obtained will be recorded on an electric database by EpiDate software at the same time, for subsequent statistical analysis.
Discussion
Depression has various clinical manifestation and insomnia is one of the most frequently occurring symptoms. Clinically, we are not simply using regulating spirit and regulating liver acupuncture formula. The formula has been optimized. Lie Que (Lu-7) and Zhao Hai (Kid-6) are two of the confluent points. The action of these two points can best be understood in relation to regulate various meridians, three Jiao, and relative organs. These two empirical points are used as the main points and subcutaneous needles are buried to consolidate the curative effects. This set of optimized formula has been well approved by clinical practice, but there is no systemic and scientific trial to evaluate its effect. The result of the trial should provide evidence-based medicine evidence for its further promotion.

Study Organization
The statistical analysis will be carried out by the DME professionals in Guangzhou University of TCM, and principle of intention to treat will be applied for the result analysis. The withdrawal or drop-out subjects will be involved into the result analysis as the original materials to fill the following gap. After approval of the protocol by the ethics Committee of Guangzhou Provincial Hospital of TCM, 2008GL-26, 2009-07-01. The trial is internationally registered at http://www.chictr.org (ChiCTR-TRC-00000481). The training working team will be established, which consist of DME professionals of Guangzhou University of TCM, staff of scientific research department and staff of General Acupuncture department. The principle institution is Guangdong Provincial hospital of TCM and the cooperative institutions are the Second People’s Hospital of Zhaoqing city and People’s Hospital of Huizhou. The data management and statistical analysis will be carried out under the guidance of DME professionals according to a prespecified statistical analysis plan. Clinical trials quality control group will be established and the investigator in each branch centre will be responsible for the quality control.

Financial support
The trial will be sponsored by the Science and Technology Planned Project of Guangdong province. The project number of funding source is 2008B030301206. The sponsor(s)’s address is located in the Scientific and Technical Information Building No 171, Lianxin Road, Guangzhou City.

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Wen-bin Fu provided general support as the head of the general acupuncture department of Guangdong provincial hospital of TCM and the leader of the trial.
Author’s contribution
Yuanfang Chen and Zhaohui Liang are responsible for the study design, definition of the primary outcomes, secondary outcomes, sample size calculation and preparation of the protocol. Nenggui Xu, Zhenghua Xu, Jianhua Liu, Wenbin Fu, Yefei Huang. Shujun Xu are responsible for the protocol alternation and consummation. Wenbin Fu is the corresponding author. All the authors have critically reviewed and approved the final version of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Competing interests
The author declares that they have no competing interest.

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