Author’s response to reviews

Title: Acupuncture for patients with mild to moderate Alzheimer's disease: a randomized controlled trial

Authors:

Yujie Jia (6062678jyj@163.com)
Xuezhu Zhang (zhangxuezhu1999@126.com)
Jianchun Yu (yujianchun1964@126.com)
Jiangxian Han (hanjingxian6@hotmail.com)
Tao Yu (doctoryutao@163.com)
Jiangwei Shi (rushk@163.com)
Lan Zhao (24300711@qq.com)
Kun Nie (349020243@qq.com)

Version: 1 Date: 28 Sep 2017

Author’s response to reviews:

Dear Editor:

Thank you for your time and patience on my manuscript entitled “Acupuncture for patients with mild to moderate Alzheimer's disease: a randomized controlled trial” (BCAM-D-17-00706).

The suggestions of reviewers are very valuable and helpful for me to revise and improve my manuscript. I has corrected the manuscript carefully and revised portion were marked in red in the paper. The response to the reviewer’s questions are shown as follows.

Thanks again.

Jianchun Yu
Reviewer 2

1. In this manuscript, the authors have conducted a randomized active controlled clinical trial to test the efficacy and safety of acupuncture for participants with mild to moderate Alzheimer’s disease. This seemed generally well conducted and this subject is of interest. However, there are some concerns on ethics and scant information on RCT conducted.

Response: The trial protocol had been approved by the Research Ethical Committee of First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (TYLL2015[K]003) on July 30, 2015 (Trial Design, Setting, Randomization and blinding Section, line 108-111, page 4). We carried out the trial protocol strictly. The manuscript has been examined carefully according to the reporting checklist of CONSORT 2010 (please see the Attach Files). We have added some information (line 91-94, page 4 and line 224-225, page 8). The reporting of the study complied with the requirements of the CONSORT 2010 statement.

2. In this reporting guideline, pre-trial registration is important, but your registration was conducted retrospectively.

Response: It is really true as reviewers suggested that pre-trial registration was very important. Because of some reasons, our trial did not register in advance. It is a pity. We retroactively registered on 18 JAN 2017 at Chinese Clinical Trial Registry (No. ChiCTR-IOR-17010465) to ensure the complete publication of all results (Trial Registration Section, line 41, page 2).

3. I am not able to agree with your conclusions which contained effective results in improving all aspects of cognitive function, global clinical status, activities of daily life and behavioral symptoms of AD. However your results seemed to support positive results only in cognitive function from ADAS-cog and clinical status from CIBIC-Plus, but not in activities of daily life from ADCS-ADL23 and behavioral symptoms from NPI. Please change your conclusions based on supportive results.

Response: The sections in Abstract and Discussion have been corrected according to the reviewer’s suggestions (line 38-39, page 2, and line 270-274, page 10).

4. The other issue is ethical one. As a research subjects for AD, as you know, AD patients are vulnerable one because they may not have normal cognitive function or an ability to make a decision by their own. Therefore, in the process of inclusion or the process of receiving
written informed consent, a legal guardian who has an alternative right to decide should be involved in those process for being double-checked or protecting human right.

Response: In this study, all patients were collected from the home visit survey. AD patients usually accompanied by their legal guardians in home and we would inform the detailed information of the study to patients and their guardians if the patients met the eligibility criteria. So, their legal guardians had a right to decide whether to participate in this study.

In the revised manuscript, I had indicated “Patients were also excluded from the study if they were incapable of giving written informed consent from the patient (or their legal representatives).” (Participants section, line 139-140, page 5).

5. For becoming more rigorous RCT,

- Please supply important time information as when finished ethical approval, when conducted clinical trial (clinical research period), when did you do trial registration, or others.

- How did you standardize nine acupuncturists?

- How did you do if when participants have had their own medications before inclusion?

- How did you do if when participants have changed their medications during the trial?

The important time information has been added in the revised manuscript, including ethical approval on July 30, 2015 (trial design section, line 117-120, page 4), clinical research period from November 2015 to May 2016 (trial design section, line 85-87, page 3), trial registration on 18 JAN 2017 (Trial Registration section, line 41, page 2).

According to the reviewer’s comments, I have added “All acupuncturists received operation instructions from professor Han, a videotape, and a brochure with detailed information on acupuncture treatment (Interventions section, line 169-171, page 6) to standardize nine acupuncturists” section.

If participants received any treatments which probably improve cognitive function within the past 1 month, they would not be enrolled in the study (trial participants section, line 136-138, page 5). If participants suffered from hypertension, coronary heart disease, the use of related drugs was allowed.

If participants received any drug to probably improve cognitive function during the entire study period, it would be not permitted (Interventions section, line 167-169, page 6). But those medications which does not improve the cognitive function would be allowed.
4. For sample size calculation in page 5. I am not able to agree with you sample size calculation. As your primary outcomes are ADAS-cog and CIBIC-plus, you should determine your sample size based on your primary outcomes. However, your calculation was conducted based on MMSE score, which seemed to me make no sense.

Response: The sample size have been recalculated according to reviewer’s suggestion (Sample Size section, line 190-197, page 7).

5. For Table 1

- Men plus women (n=79) makes no 87 (total participants).
- Also all men (n=27) differ from acupuncture (n=12) plus Donepezil (n=14).- Please check you whole data from Table 1.

Response: The data in table 1 have been examined carefully.

Minor Essential Revision

1. Abstract

- Please check your abbreviations in abstract. There were no full name of AG, DG.

Response: The full name of AG, DG has been added in the revised manuscript (Abstract section, line 20-22, page 1).

2. In introduction, page 2

- effectiveness, line 58 -> efficacy
- Please check another related systematic review [1].

Response: The word “effectiveness” has been corrected to “efficacy” (background section, line 78, page 3). In addition, the results of another related systematic review has been added in the manuscript according to the reviewer’s suggestions (background section, line 79-80, page 3).

3. Please check you typo.

- Table 1, Donepezi -> Donepezil

- Table 1, Moderaten -> Moderate

- ASAS-COG, in Figure 2 -> ADAS-COG

Response: The word “Donepezi” has been corrected to “Donepezil” (table 1), “Moderaten” to “Moderate” (table 1), and “ASAS-COG” to “ADAS-COG” (Figure 2).

7. Please check abbreviations. Please define it at its first appearance, if defined, please use the defined one.

- MMSE, ADL in page 3

Response: The word “MMSE” has been corrected to “Mini-mental State Examination, MMSE” (Participants section, line 118, page 4), and “ADL” has been corrected to “Activity of Daily Living scale, ADL” (Participants section, line 118-119, page 4).