

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Chinese herbal medicine Jian Ling Decoction for essential hypertension: A systematic review and meta-analysis of randomized controlled trials
AUTHORS	Xiong, Xing-jiang; Wang, Pengqian; Li, Xiaoke; Zhang, Yuqing

VERSION 1 - REVIEW

REVIEWER	Adrian Barnett Queensland University of Technology, Australia
REVIEW RETURNED	12-Sep-2014

GENERAL COMMENTS	<p>This study uses meta-analysis to show a reasonably consistent benefit of Jian Ling Decoction in combination with antihypertensive drugs.</p> <p>What is the mechanism for the combined therapy of JLD and antihypertensive drugs? For example, does it interact with the antihypertensive drugs in some way, or does it reduce the side-effects meaning that people are more likely to adhere to their antihypertensive drugs? Why did so many of the previous studies examine JLD in combination with antihypertensive drugs.</p> <p>The control groups are very heterogeneous in terms of what they received. This seems worthy of comment.</p> <p>Reasons should be given for the decision to include trials where JLD was given in combination with antihypertensive drugs, but exclude trials where it was given with other interventions (page 9).</p> <p>Page 9, "Duration of treatment was at least 2 weeks." Is this another inclusion criteria? It would make the paper clearer if all the inclusion and exclusion criteria were first listed, followed by the reasoning behind the decisions.</p> <p>The search strategy did not include the alternative spelling of "randomised controlled trial".</p> <p>Minor comments</p> <ul style="list-style-type: none">- Abstract, suggested edit: "The primary outcome was categorical or continuous blood pressure (BP)"- Page 5, line 27, suggested edit: 'was discovered' not 'has been discovered'- Page 5, line 46, can you be specific about the undesirable effects?- Page 6, line 4, one of the most common compared with what?- Page 6, line 26, should 'dispensed by' be 'invented by'?- Page 9, line 11, 'included' instead of 'considered'? and 'were' instead of 'should be'.
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	<ul style="list-style-type: none"> - Page 10, line 39, was it the authors who resolved disagreement issues? - Page 11, line 49, 'found' not 'got' - Page 12, line 4, don't need 'the' in front of 'publication bias' - Page 14, line 29, 'withdrawals' - Page 15, line 49, 'measured' not 'applied' - Page 16, line 29, 'might improve' not 'can improve' - Page 19, fourth paragraph, where are the results of "the quality of evidence for BP outcome"? I can see the overall estimates of study quality, but nothing specific on BP. - Page 19, line 49, 'become a concern' rather than 'become widely concerned' - Figure 1, 'inclusion' not 'inclusive' criteria - The Figure 2 legend should state that this is categorical BP; I would narrow the x-axis range to remove a lot of the white space. - The Figure 3 legend or axis label should mention the units of measurement (mmHg?)
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REVIEWER	Arthur de Sá Ferreira Centro Universitário Augusto Motta, Brazil
REVIEW RETURNED	17-Sep-2014

GENERAL COMMENTS	<p>This is a well-conducted systematic review and meta-analysis on the effects of Jian Ling Decoction in patients with essential hypertension. The study appears justified and the methods are clearly reported and sound. All requirements for systematic reviews and meta-analysis were reported according to the PRISMA statement (including but not limited to the database search strategies, flowchart, risk of bias assessment, and PRISMA checklist). I have one comment to which I would like the authors to elaborate their Discussion.</p> <p>Major review:</p> <p>1) Results concerning studies comparing JLD <i>versus</i> antihypertensive drugs and JLD plus antihypertensive drugs <i>versus</i> antihypertensive drugs alone are interesting. For instance, consider the diastolic blood pressure outcome. In the one hand, the criterion for "significant improvement" or "improvement" are fuzzy-like, but it might be fair to state that it includes a 10-mmHg decrease in diastolic blood pressure (n=170 cases). On the other hand, the WMD was -6.71 mmHg for DBP (n=485 cases). Collectively, these results could be interpreted as similar because of both lower statistical power in tests with categorical variables as compared with tests with continuous ones and a small sample size in the former case and a larger sample size in the latter case. Therefore, could it be argued that such differences in outcome are indeed statistical but no clinical?</p> <p>Minor review:</p>
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	2) References, page 26: Reference #37 has a typo ('square' symbol).
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REVIEWER	GUO-QING ZHENG Department of neurology, the second affiliated hospital of Wenzhou Medical University, China
REVIEW RETURNED	28-Sep-2014

GENERAL COMMENTS	<p>I am grateful to have the opportunity to review the study titled "Chinese herbal medicine Jian Ling Decoction for essential hypertension: a systematic review and meta-analysis of randomized controlled trials" for BMJ Open. In this manuscript, the authors performed a systematic review and meta-analysis based on 10 RCTs to assess the efficacy and safety of Jian Ling Decoction (JLD) for essential hypertension (EH). This is a well performed systematic review followed by the PRISMA.</p> <p>Major Compulsory Revisions</p> <p>1. Given the lack of high quality studies, the claim of "some encouraging clinical evidence of JLD as a kind of complementary therapy for EH was found" is not supported by the results from this review.</p> <p>2. The major issue that the authors need to better address is the justification for performing the meta-analyses given that the included studies were of small size, poor methodological quality and possessed a high risk of bias.</p> <p>Minor Essential Revisions</p> <p>JLD is a very complex preparation. All species need to be validated taxonomically (e.g. www.theplantlist.org) and the full name including authorities and family needs to be included. It is important to identify the level of detail about the composition of the preparations and you should critically appraise the status of this in the original articles included.</p> <p>Discretionary Revisions</p> <p>P 5, line 26-29, Yi Xue Zhong Zhong Can Xi Lu (also named as Integrating Chinese and Western Medicine); authors may consider using "Yixue Zhongzhong Canxilu (Records of Traditional Chinese in Combination with Western Medicine)" .</p>
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REVIEWER	Shung-Te Kao School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan, Republic of China
REVIEW RETURNED	06-Oct-2014

GENERAL COMMENTS	<p>This article used systematically reviewed of seven electronic databases to assess the current clinical evidence of Jian Ling Decoction for essential hypertension. The author indicated that JLD is a kind of complementary therapy for EH.</p> <p>The paper can be accepted for publication.</p>
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VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer #1 Adrian Barnett

1. This study uses meta-analysis to show a reasonably consistent benefit of Jian Ling Decoction in combination with antihypertensive drugs. What is the mechanism for the combined therapy of JLD and antihypertensive drugs? For example, does it interact with the antihypertensive drugs in some way, or does it reduce the side-effects meaning that people are more likely to adhere to their antihypertensive drugs? Why did so many of the previous studies examine JLD in combination with antihypertensive drugs.

Response: Thank you very much. Jian Ling Decoction (JLD) is a famous classic herbal formula in traditional Chinese medicine. It is often prescribed to improve hypertension-related symptoms in China. Currently, as effective western medicine treatments are available for hypertension, TCM is often used in addition to baseline treatment with western medicine to enhance the hypotensive effect and reduce the toxicity of conventional treatment. That is, patients in control group received conventional western medicine therapy alone, while patients in treatment group received a combination of TCM and western medicine therapy. This is also known as an add-on design, which is quite popular for TCM studies of various diseases and conditions [ref. 1-5]. Therefore, TCM physicians often used JLD in combination with antihypertensive drugs to achieve greater improvement in the signs and symptoms of hypertension and to enhance the antihypertensive effect of conventional drugs with less adverse effects. In four Chinese databases, a large number of studies (case reports, case series, non-RCTs, and RCTs) examined the effect of JLD in combination with antihypertensive drugs for the treatment of hypertension. We have revised it in the “introduction” section (P7-8).

Ref. 1-5

1. Mao C, Chung VC, Yuan JQ, Yu YY, Yang ZY, Wu XY, et al. Evaluation of the add-on effect of Chinese patent medicine for patients with stable or unstable angina: a systematic review and meta-analysis. *Evid Based Complement Alternat Med* 2013; 2013: e673193, 1-15.
2. Chang C. Is integrative medicine the next new frontier in medicine?. *Clin Rev Allergy Immunol* 2013; 44: 205-207.
3. Tsang IK. Establishing the efficacy of traditional Chinese medicine. *Nat Clin Pract Rheumatol* 2007; 3: 60-61.
4. Bell IR, Caspi O, Schwartz GE, Grant KL, Gaudet TW, Rychener D, et al. Integrative medicine and systemic outcomes research: issues in the emergence of a new model for primary health care. *Arch Intern Med* 2002; 162: 133-140.
5. Wong R, Sagar CM, Sagar SM. Integration of Chinese medicine into supportive cancer care: a modern role for an ancient tradition. *Cancer Treat Rev* 2001; 27: 235-246.

2. The control groups are very heterogeneous in terms of what they received. This seems worthy of comment.

Response: Thank you very much. All of the patients in the control groups received antihypertensive drug treatment, including felodipine, nifedipine, enalapril, and benazepril hydrochloride. As you say, interventions in control groups are very heterogeneous. Therefore, we analyzed the heterogeneity of the included trials in the “discussion” section (P20).

3. Reasons should be given for the decision to include trials where JLD was given in combination with antihypertensive drugs, but exclude trials where it was given with other interventions (page 9).

Response: Thank you very much. We have revised it in the “Types of interventions” section with red color (P10). Detailed information could also be found as below: “However, trials assessing the combined effect of JLD with other interventions (e.g., another CHM, qigong, Tai Chi, acupuncture, moxibustion and massage) were excluded given that the therapeutic effect of JLD could not be distinguished.”

4. Page 9, "Duration of treatment was at least 2 weeks." Is this another inclusion criteria? It would make the paper clearer if all the inclusion and exclusion criteria were first listed, followed by the reasoning behind the decisions.

Response: Thank you again. We have added it in the "Types of interventions" section with red color (P10).

5. The search strategy did not include the alternative spelling of "randomised controlled trial".

Response: Thank you again. We have added it in the "Search strategies" section with red color (P9).

6. Abstract, suggested edit: "The primary outcome was categorical or continuous blood pressure (BP)".

Response: Thank you again. We have added it in the "Abstract" and "Types of outcome measures" sections with red color (P2, 11).

7. Page 5, line 27, suggested edit: 'was discovered' not 'has been discovered'.

Response: Thank you again. We have revised it in the "introduction" section with red color (P6).

8. Page 5, line 46, can you be specific about the undesirable effects?

Response: Thank you again. We have revised it in the "introduction" section with red color (P6).

9. Page 6, line 4, one of the most common compared with what?.

Response: Thank you again. We have revised it in the "introduction" section with red color (P7).

10. Page 6, line 26, should 'dispensed by' be 'invented by'?

Response: Thank you again. We have revised it in the "Types of participants" section with red color (P10).

11. Page 10, line 39, was it the authors who resolved disagreement issues?

Response: Thank you again. We have revised it in the "Data extraction" section with red color (P12).

12. Page 11, line 49, 'found' not 'got'.

Response: Thank you again. We have revised it in the "Data synthesis" section with red color (P13).

13. Page 12, line 4, don't need 'the' in front of 'publication bias'.

Response: Thank you again. We have revised it in the "Data synthesis" section with red color (P13).

14. Page 14, line 29, 'withdrawals'.

Response: Thank you again. We have revised it in the "Methodological quality" section as "Drop-out and withdrawal data were provided for three trials" (P15).

15. Page 15, line 49, 'measured' not 'applied'.

Response: Thank you again. We have revised it in the "result" section with red color (P17).

16. Page 16, line 29, 'might improve' not 'can improve'.

Response: Thank you again. We have revised it in the "Secondary outcome: QOL" section with red color (P17).

17. Page 19, fourth paragraph, where are the results of "the quality of evidence for BP outcome"? I can see the overall estimates of study quality, but nothing specific on BP.

Response: Thank you for this helpful suggestion. Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE), we assessed the quality of evidence for BP outcome. It was classified as "low". After checking the article again, it was found that the fourth

paragraph on P19 contained some duplicate information from “results” section. Thus, in this revision, we have deleted it (P20).

18. Page 19, line 49, 'become a concern' rather than 'become widely concerned'.

Response: Thank you again. We have revised it in the “Limitations” section with red color (P21).

19. Figure 1, 'inclusion' not 'inclusive' criteria.

Response: Thank you again. We have revised it in Figure 1.

20. The Figure 2 legend should state that this is categorical BP; I would narrow the x-axis range to remove a lot of the white space.

Response: Thank you again. We have revised it in Figure 2.

21. The Figure 3 legend or axis label should mention the units of measurement (mmHg?)

Response: Thank you again. We have revised it in Figure 2.

Responses to the comments of Reviewer #2 Arthur de Sá Ferreira

1. Results concerning studies comparing JLD versus antihypertensive drugs and JLD plus antihypertensive drugs versus antihypertensive drugs alone are interesting. For instance, consider the diastolic blood pressure outcome. In the one hand, the criterion for “significant improvement” or “improvement” are fuzzy-like, but it might be fair to state that it includes a 10-mmHg decrease in diastolic blood pressure (n=170 cases). On the other hand, the WMD was -6.71 mmHg for DBP (n=485 cases). Collectively, these results could be interpreted as similar because of both lower statistical power in tests with categorical variables as compared with tests with continuous ones and a small sample size in the former case and a larger sample size in the latter case. Therefore, could it be argued that such differences in outcome are indeed statistical but no clinical?

Response: Thank you very much. The primary outcome analyzed for this meta-analysis was categorical or continuous BP. For categorical BP, risk ratio (RR) was used in this review. However, there are limits to the evaluation criteria, although it was authoritatively recommended by China Food and Drug Administration. It defined the effect on categorical BP as “significant improvement”, “improvement”, and “no improvement”. We also tried to contact the primary authors for detailed information about BP data before and after treatment. However, all of the studies did not report contact information (telephone, e-mail, fax) about the corresponding author, and nothing could be got. In my opinion, it did weaken the strength of evidence for global acceptance. Thus, further studies should pay more attention to the reporting of continuous BP. Only in this way, the real effect of Chinese herbal medicine in treatment of hypertension can be evaluated objectively. For continuous BP, meta-analysis was conducted based on the reported data about SBP and DBP. Due to the insufficient clinical data, poor methodological design, and high risk of bias, it is difficult to draw a definite conclusion regarding the effectiveness and safety of JLD for EH. More rigorously designed trials are needed.

2. References, page 26: Reference #37 has a typo (‘square’ symbol).

Response: Thank you for this helpful suggestion. We have revised it as “Guan DM, Du SQ. Clinical observation on the effect of jian ling decoction combined with urapidil on stage III hypertension with high-risk. Zhongguo She Qu Yi Shi 2013; 15: 214-215.”

Responses to the comments of Reviewer #3 GUO-QING ZHENG

1. Given the lack of high quality studies, the claim of “some encouraging clinical evidence of JLD as a kind of complementary therapy for EH was found” is not supported by the results from this review.

Response: Thank you for this helpful suggestion. We have revised the conclusion with red color (P21). Detailed information was listed as follows:

“Due to the insufficient clinical data, poor methodological design, and high risk of bias, it is difficult to

draw a definite conclusion regarding the effectiveness and safety of JLD for EH. More rigorously designed trials according to the CONSORT Statement are needed.”

2. The major issue that the authors need to better address is the justification for performing the meta-analyses given that the included studies were of small size, poor methodological quality and possessed a high risk of bias.

Response: Thank you for requesting this important clarification. We have revised the conclusion with red color (P21).

3. JLD is a very complex preparation. All species need to be validated taxonomically (e.g. www.theplantlist.org) and the full name including authorities and family needs to be included. It is important to identify the level of detail about the composition of the preparations and you should critically appraise the status of this in the original articles included.

Response: Thank you again. As suggested, we have confirmed all the Chinese herbal medicine used in JLD based on the international website and pharmacy dictionary with authority. English name, Pinyin, and Latin name of each Chinese herbal medicine was provided in the article.

4. P 5, line 26-29, Yi Xue Zhong Zhong Can Xi Lu (also named as Integrating Chinese and Western Medicine); authors may consider using “Yixue Zhongzhong Canxilu (Records of Traditional Chinese in Combination with Western Medicine)”.

Response: Thank you for this valuable suggestion. We have revised it in the “introduction” section (P7).

Responses to the comments of Reviewer #4 Shung-Te Kao

1. This article used systematically reviewed of seven electronic databases to assess the current clinical evidence of Jian Ling Decoction for essential hypertension. The author indicated that JLD is a kind of complementary therapy for EH. The paper can be accepted for publication.

Response: Thank you for your kind observations and recommendation.

In summary, we have learned so much through revising this article again under the guidance of experts' kind help and suggestions. I am looking forward to get further guidance from you. Thank you very much.

VERSION 2 – REVIEW

REVIEWER	Guo-qing Zheng Department of neurology, the second affiliated hospital of Wenzhou Medical University
REVIEW RETURNED	08-Nov-2014

GENERAL COMMENTS	I'm satisfied with all the responses.
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VERSION 2 – AUTHOR RESPONSE

Responses to the comments of Reviewer Guo-qing Zheng

1. I'm satisfied with all the responses.

Response: Thank you very much.

In summary, I have learned so much through revising this article again under the guidance of experts' kind help and suggestions. I am looking forward to get further guidance from you. Thank you very much.