Author's response to reviews

Title: Sertraline plus deanxit to treat patients with depression and anxiety in chronic somatic diseases: a randomized controlled trial

Authors:

Limin Wang (wanglimingd@126.com)
Zhuoyuan Zhong (zzhuoyuan@163.com)
Jingyang Hu (15913192315@126.com)
Xiaoming Rong (irisrong1227@hotmail.com)
Jun Liu (13609794537@126.com)
Songhua Xiao (songhuaxiao@aliyun.com)
Zhonglin Liu (13719438236@126.com)

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Author's response to reviews: see over
Dear Mr. Carlo Rye Chua,

Thank you very much for arranging a timely review for our manuscript. We feel deeply grateful to editors and reviewers for thoughtful and constructive comments and suggestions on our manuscript entitled "Sertraline plus deanxit to treat patients with depression and anxiety in chronic somatic diseases: a randomized controlled trial" (ID 7804752551453087).

We have studied the comments carefully and tried our best to revise and improve the manuscript according to the reviewers’ good comments. We earnestly appreciate for Editors/Reviewers’ warm work, and hope that the corrections will meet with approval. Please feel free to contact us with any questions and we are looking forward to your consideration. Revised portions are marked in red in the paper and responds to the reviewers’ comments are as follows:

Responds to the reviewer’s comment:

To reviewer #1:

1. How was the dosing schedule chosen (for both sertraline and deanxit)?

Response: We assigned patients to either deanxit group or placebo group: sertraline (75mg/day) plus deanxit (one piece/day) (N=38), or sertraline (75mg/day) plus placebo (one piece/day) (N=37) for 2 weeks, both
groups received sertraline (75mg/day) in the following 2 weeks. In briefly, deanxit group: both sertraline and deanxit (2 weeks) + sertraline(2 weeks); placebo group: both sertraline and placebo (2 weeks) + sertraline(2 weeks).

2. Given the wide age range and inclusion of older patients, was any consideration given to adjustments in dosing and/or tapering?

Response: It is true that more consideration should be given owing to inclusion of older patients. According to a meta-analysis published in Lancet, 75mg sertraline is quite a low dose and dosages often rang from 50mg to 200mg clinically. Considering the safety, we employed only one dose without any adjustments in a rather conservative way.

3. Why was deanxit discontinued after only 2 weeks?

Response: Sertraline can exert effect in the third week generally, while deanxit is designed for short term usage, improving mood illness to some extent when prescribed in low dose for a short period of time, thus compensating the shortage of delayed response of sertraline. Besides, long-term use of deanxit may result in adverse events.

4. What was the rationale for completing HAM-A and HAM-D on Day 1, 4, 8, 15, 29?

Response: Firstly, the comparability of the baseline scores in HAM-A and HAM-D between two groups should be confirmed on day 1. Secondly, it was reported that deanxit might work on emotional disorders
in 3-5 days, thus comparisons on day 4 was a suitable choice. Thirdly, the assessments on day 8 and day 15 were conducted for the reason that the effect would be obvious during the first and second week. Lastly, follow-up should be administered and the scores should be recorded to observe whether deanxit displayed a long-term effect after discontinuation.

5. Regarding analyses, it would be helpful to include more information about changes in HAM-A and HAM-D scores. For example, perhaps a table could be included that lists means and standard deviations at each time point and/or includes the rates of “recovery,” “significant improvement,” “improvement” and “lack of improvement.” Only comparing rates of >25% improvement offers somewhat limited value.

Response: We genuinely endorse this viewpoint for it is quite rational. However, there are limited numbers of subjects in the study, as well as the distinct variations among individuals in HAM-A and HAM-D scores, hence the therapeutic efficacy may not be reflected accurately. Given the above mentioned, we have not compared the other rates statistically.

6. The manuscript would benefit from careful editing by a native English speaker (to correct grammar, vocabulary, etc.). There appears to be a lack of commas throughout the manuscript, which makes the text more difficult to read.

Response: We are very sorry for our negligence of the shortage in the
written skills and the lack of commas. Accordingly, a native English speaker have edited the whole manuscript sentence by sentence as well as the commas added appropriately.

7. The introduction is concise, but might benefit from inclusion of additional information about deanxit (e.g., half-life of the medication). Some of the studies reviewed in the discussion may be more useful to include in the introduction to assist readers who may be less familiar with deanxit.

**Response:** It is really true that more information should be added to the introduction to assist readers know more about deanxit, thus we added the relevant content to the background section.

*Related changes as follows:*

**Background section:**

The biological half-life of flupentixol is about 35 hours and melitracen is about 19 hours, and the drugs show synergistic effect on therapeutic administration and antagonistic effect on adverse reaction. The combination of two psychoactive agents which has antidepressant properties is designed for short term usage only. According to published evidences, melitracen/flupentixol combination is the most frequently prescribed compound on the basis of defined daily doses in China [16]. Deanxit can improve mood illness to some extent when prescribed in low dose for a
short period of time, thus compensating the shortage of delayed response of sertraline. More generally, during the no response time for at least two weeks, deanxit is well tolerated.

8. In the discussion, the authors make the case that it often takes 2-3 weeks for clinical benefit from SSRI medication—clinical experience suggests this delay can last much longer. In addition, optimal dosage ranges from 50-200mg/day within individuals. It would be helpful to discuss the results in this context.

Response: Generally, antidepressant dosages for therapeutic use in anxiety and depression with somatic diseases are relatively lower in comprehensive hospital in China. The subjects in our study are the individuals in depression and anxiety with chronic somatic diseases. Considering for the potential adverse reactions, we apply low dosage in the study. Moreover, our research indicates that deanxit can heighten the effect of SSRIs to some extent, and for which reason, addition of deanxit with SSRIs during an early phase can achieve a rapid onset and an excellent efficacy.

9. The relevance of the paragraph on page 28-29 describing efficacy of sertraline was unclear. Perhaps this information would be more useful in the introduction?

Response: We have mentioned the clinical efficacy as a whole in the background part. Besides, revise has been made to show the efficacy in
Referring to a meta-analysis of 12 new-generation antidepressants, the cumulative probabilities of efficacy and acceptability of sertraline are 20.3% and 21.3%[^12].

To reviewer #2

1. It’s not a good choice because of its potential side effects. This drug is banned in USA also. How would this study be of interest to USA audience? Also based on this more information is needed about why it is banned in USA and about the side effects.

Response: According to the viewpoint of an assistant professor in India about the ban of deanxit, there is no credible agency in the government sector that critically evaluates available literature to know the safety profile of the drug. We speculate that USA bans the drug over safety concerns. Generally, in terms of safety profile, long-term use of deanxit may develop tardive dyskinesia and tardive akathisia, which should be highlighted to be aware of withdrawal of deanxit without delay, thus avoiding severe adverse events in movement. We should pay attention to the movement side effects induced by this combined antidepressant/antipsychotic medication, especially for long-term use in depressed patients.

Nowadays, deanxit is the most frequently prescribed compound on the basis of defined daily doses in China[^16]. Deanxit can improve mood
illness to some extent when prescribed in low dose for a short period of time. More generally, during the no response time for at least two weeks, deanxit is well tolerated for no obvious adverse reaction is detected. However, long-term use may result in adverse reaction which can be avoided or reversed by discontinuation in time.

Special thanks to you for your good comments.

We have tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we have not listed all of the changes. Finally, we would like to express our great appreciation to you and reviewers for the comments on our paper. Looking forward to hearing from you soon.

Thank you and best regards.

Yours sincerely,

Zhuoyuan Zhong  E-mail:zzhuoyuan@163.com

Corresponding author:

Name:Zhonglin Liu    E-mail:zhonglinliu@126.com