Author’s response to reviews

Title: Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo controlled clinical trial

Authors:

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Version: 4 Date: 23 January 2015

Author’s response to reviews: see over
Dear editors-in-Chief: Doug Altman, Curt Furberg, Jeremy Grimshaw

thank you for your comments regarding the manuscript (MS: 1699861555136750) entitled as:
Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo controlled clinical trial
Ali sahraian, Ahmad Ghanziadeh and Feresteh Kazemeini
The manuscript is revised as follow:

<table>
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<tr>
<th>Editorial requests:</th>
<th>Corrections</th>
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<tr>
<td>1. Please include the email addresses of all authors on the title page.</td>
<td>Those are added.</td>
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<tr>
<td>2. Please include the date of registration with the trial registration number at the end of the Abstract.</td>
<td>Those are added.</td>
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<tr>
<td>3. Your current Acknowledgements section appears to contain the Authors' Contributions section, so please rename this as 'Authors' Contributions', and also state that all authors read and approved the final manuscript.</td>
<td>Corrected and added.</td>
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<tr>
<td>4. Please include a separate Acknowledgements section after the Authors' Contributions section, and state clearly whether or not you have funding here. If there is no funding, please state this.</td>
<td>Added.</td>
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<td>5. Please move the tables below the reference list.</td>
<td>Moved.</td>
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<td>6. Please include figure 2 in the figure legend section.</td>
<td>Included.</td>
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**Reviewer’s report**

**Title:** Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo controlled clinical trial

**Version:** 3  
**Date:** 23 November 2014  
**Reviewer:** Mattie Tops

**Reviewer’s report:**

The authors were responsive to most comments.

- **Major Compulsory Revisions**

- **Minor Essential Revisions**

1. In general, the writing and spelling still needs checking, including in newlyadded parts.  

   Checked.
2. Background
First paragraph: The general public is not familiar with enzymes/compounds such as “glutathione reductase” and “glutathione peroxidase”. Their relevance needs explaining, e.g., as being markers of oxidation. Also, the first paragraph now refers to “ascorbic acid” but it is not explained that this is also known as water-soluble vitamin C. Despite this, the first paragraph also refers to vitamin C.

- Discretionary Revisions
  Minor issues not for publication

3. I suspect that this journal adheres to the convention of reporting two numbers after the decimal point for p values, even when the second is zero. Editor?

4. Background, second paragraph, second sentence first word should be capitalized. Two sentences further: “decreases” should be “decrease”.

5. The final-but-one paragraph of the Background is only two sentences long.

**Level of interest:** An article of importance in its field

### Reviewer's report
**Title:** Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo controlled clinical trial
**Version:** 3  
**Date:** 2 December 2014  
**Reviewer:** Manuella P Kaster

**Reviewer's report:**
In my point of view there were great improvements in the new version of the manuscript. The authors addressed the points raised by the referees and the discussion is much better in this revised version. I still have some considerations especially in the organization of the introduction. My suggestions are listed below.

**Minor essential revisions:**
Abstract
There is a spelling mistsken in line two... depressive.
In the conclusion the word acid after citalopram should be removed.
I think that the authors should standardize the use of vitamin C or ascorbic acid in the manuscript.

Corrected.

Background

I still think that the introduction is confusing. The authors should start with a more general sentence... for example: In the past decades, several clinical and pre-clinical works reported that changes in oxidative stress parameters and in the activity of antioxidant enzymes might be involved in pathophysiology of MDD. In addition, it always should be mention if the work is clinical or pre-clinical and evidence in humans and animal models should be organized.
In the first sentence... the authors should add ... are increased in major depressive disorder patients”... to highlight that this is a clinical work. In the second sentence... this result is in an animal model of depression induced by stress? Is the activity of SOD increased or decreased by stress? In the third sentence... the authors should change “in the animal” for in pre-clinical models.
In the end of first paragraph... references 3 and 4 are in patients with MDD? This should be described in the sentence.

Revised and added.

The authors should reorganize this section: “Ascorbic acid the same as fluoxetine reverses brain oxidative damage [7]. Antidepressants may decrease the increased level of oxidative stress in MDD patients [8]. Treating MDD with fluoxetine and citalopram decreased the increased levels of SOD and serum MDA [1].” In my suggestion it would be better: Antidepressants are capable to reverse the changes in oxidative stress parameters in MDD patients. A clinical trial demonstrated that the peripheral activity of the antioxidant enzyme SOD and the levels of the oxidative marker MDA were higher in MDD patients. These changes were accompanied by a reduction in the levels of ascorbic acid and were reverted after the

Revised.
treatment with fluoxetine and citalopram, further reinforcing the role of ascorbic acid in the MDD [1]. In addition, ascorbic acid had an effect similar to fluoxetine in an animal model of depression, reverting not only the behavioral profile induced by stress but also the oxidative damage [7].

“There are some promising reports about the effect of vitamin C for treating depression in animals.” This statement should be change since animal models are never considered depression in animals. Please change to...

There are some promising reports about the beneficial effect of vitamin C in animal models of depression. Nevertheless, supplementary vitamins C (1000 mg/day) did not decrease depression in type 2 diabetic patients in a randomized, single-blind, placebo-controlled trial [15]. The authors should change depressi

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<th>An article of importance in its field</th>
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<tr>
<td>Quality of written English:</td>
<td>Needs some language corrections before being published</td>
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<tr>
<td>Statistical review:</td>
<td>No, the manuscript does not need to be seen by a statistician.</td>
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<tr>
<td>Declaration of competing interests:</td>
<td>I declare that I have no competing interests.</td>
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Reviewer's report
Title: Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo controlled clinical trial
Version: 3 Date: 21 November 2014
Reviewer: Andrew Hugh Ford

Reviewer's report:
Thank you for asking me to re-review this manuscript following the changes implemented by the authors. The manuscript looks a lot better although there are still a few issues:

- The sentence in the abstract has been re-worded but should be “We also checked for the presence of adverse effects.”
- The introduction is a little better but still has a

Corrections

The first paragraph is revised.
number of phrasing issues e.g. the third sentence “...in the animal.”, sentence 2, page 5 “...increased mood.” I personally think that the first chapter should be deleted.  

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<th>according to one of the reviewers' comments.</th>
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<td>• The hypothesis is a good addition but is incorrectly phrased. It could be written as: “We hypothesized that vitamin C would augment the antidepressant effect of citalopram in treating adult patients with major depressive disorder.”</td>
<td>Changed.</td>
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<td>• The randomization issue has not been satisfactorily clarified. The authors state in their letter that “Their participation was voluntary” yet in the manuscript they state that 68 patients were randomly allocated into the 2 groups (35 and 33) but then 25 patients “declined to participate”. Why were they randomized if they did not consent?</td>
<td>They withdrew their participation.</td>
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**Level of interest:** An article of importance in its field

Please let me know if more corrections are needed. Those will be done as soon as possible and as much as needed.

Best