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OPEN PEER REVIEW

Evaluation of Clonidine Augmentation Therapy for Obsessive-Compulsive Disorder Treatment; a Randomized Clinical Trial

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

5 comments · 29 Dec 2020 – 14 Jan 2021

Referee 1 Reviewer

MINOR REVISION 29 Dec 2020

1. This article is not described as a random trial in the title.
2. It is not clear who made the definitive diagnosis.
3. It is not explained how the sample size was determined.
4. It is not explained how the initial dose was determined.
5. It is not explained which studies determine the maximum dose.
6. It does not specify the basic demographic and clinical characteristics of each group and the relationship between these characteristics and the results.
7. It does not address the generalizability of the trial findings.
8. It does not identify the trial's limitations.

Referee 2 Reviewer

MAJOR REVISION 1 Jan 2021

The authors evaluated the effect of clonidine on the treatment of patients with refractory OCD. It is an interesting idea. However, I am concerned about several issues in this paper.
Title
1) The title should be revised. According to the CONSORT recommendation, it is worthwhile to note "randomized clinical trial" in the title.
Abstract
2) State p values clearly.
3) State the length of follow-up.
Introduction
4) Mention previous research addressing this problem.
5) Please clarify the objectives.
6) State primary and secondary outcomes.
Materials And Methods
7) How did the authors select participants?
8) What is the definition of refractory cases?
9) How did the authors estimate an adequate sample size?
10) How was this research blinded? The adverse effects of clonidine can interfere with blinding.
11) State the IRCT registry number. This proposal received ethical approval on 2018/10/08. However, the authors recruited OCD participants from May 2016.
12) DSM-V-TR?
13) The authors cited an inappropriate reference (number 6) for the severity criterion.
14) How did the authors conduct block randomization? State this in detail.
15) Describe the measurement tools.
16) When was clonidine given?
17) The authors explained that 1 mg/day of clonidine is the maximum dose of clonidine for psychiatric disorders. However, the Hewelett study showed that 1 mg/day of clonidine is ineffective in patients with OCD.
18) How was the normality of the data distribution checked?
19) Identify where the Benferroni correction was used.
Results

20) In the Results section, the demographic characteristics of the two groups should be noted.
21) The z scores for different parts of mapping before and after the intervention, the 95% confidence intervals for the differences, and the p values should be mentioned.
22) In total, 1 out of 30 participants was lost to follow-up in the case group due to adverse effects of clonidine. It is necessary to consider this case.
23) Draw a CONSORT flowchart.
24) The statistical analyses are incorrect. How did the authors control for covariates or confounders?
Discussion
25) Explain the possible mechanisms of clonidine's effect on OCD.
26) It is better to say "This research showed the enough evidence to reject null hypothesis".
27) State the strengths and limitations.
References
28) There are only five references from the last 5 years.

Referee 3 Reviewer

MAJOR REVISION 7 Jan 2021

The study method is acceptable, by and large, although there are some issues with the submitted manuscript, which are listed below:
1. "psychological" should be replaced with "neuropsychiatric" in the first sentence of the abstract.
2. "YALE-BROWN OBSESSIVE COMPULSIVE SCALE (Y-BOCS)" should use standard capitalization. In addition, the duration of the trial should be mentioned in the abstract.
3. One or two sentences about the basic biological theory of the trial should be added to the abstract.
4. The mean difference for each group and the mean scores before and after the intervention should be mentioned in the abstract.
5. The type of study should be mentioned in the title.
6. The biological theory of the trial, as well as other etiological theories of OCD, such as glutamate, serotonin and neuroinflammation, should be described in both the introduction and discussion, and the findings of the current study should be compared with those of previous studies.
7. "The current study is a double-blinded randomized-clinical-trial conducted on 57 obsessive compulsive diseases based on Clinical Neuropsychiatry 2013" is not clear at all. What is Clinical Neuropsychiatry 2013?
8. What does DSM-V-TR mean in the method section?
9. The dosage of clonidine seems to be higher than usual. The authors should explain how many pills were prescribed daily. How was the participants' blood pressure assessed?
10. The Method section should be rewritten in a structured format.
11. The IRB code and IRCT code should be mentioned.
12. "From the rater group..." is from the text. What does rater group mean?
13. Based on table-1, it seems that improvement in the clonidine group is significantly greater than in the placebo group. If so, the trial should be reported as a positive finding in all parts of the manuscript, more specifically the abstract.
14. The higher frequency of side effects in the clonidine group should be emphasized in the abstract as well.
15. Previous studies should be explained in more detail in the discussion to allow comparison.

Associate Editor

MAJOR REVISION 8 Jan 2021

Dear authors
According to the reviewers' comments, this paper needs a major revision. Please find the comments and let us

have your revised manuscript.
best
AE

Editor-in-Chief

MAJOR REVISION 14 Jan 2021

Your paper has been evaluated by external peer reviewers. Please revise your paper according to the reviewers' comments. I would appreciate it if you could make the revisions as soon as possible using Track Changes mode in MS Word and colored text.

After revision, authors are obliged to upload a Word file containing the reviewers' comments and their responses to all comments, one by one.

Besides, please pay attention to the word count limitation:
Word count limits are declared in this link: http://kowsarpub.com/en/index.php/services/for-authors/895-word-count

We look forward to receiving your revised manuscript. Thank you for sending your work to the Iranian Journal of Psychiatry and Behavioral Sciences.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Revisions:

Reviewer 1:

1.This article is not described as a random trial in the title.

- Thank you for your recommendation.. The phrase randomized clinical trial has been added to the tilte

2.It is not clear that who made the definitive diagnosis?

- Thank you for your recommendation. It has been done. Page 3, paragraph 1, lines 1 and 2,

3.It is not explain that how sample size was determined?

- Thank you for your recommendation. It has been done. Page 2, the last paragraph

4.It is not explain that how determined the initial dose?

- It has been presented that the dosages including the initial and the maximal doses were derived from the study conducted by Helewet et al.. Due to the paucity of knowledge regarding the dosage of clonidine for OCD, we administered a similar intial dose to what was used by Helewet study. page 3, paragraph 2

5.It is not explain that which studies determine the maximum dose.

- It has been presented that the dosages including the initial and the maximal doses were derived from the study conducted by Helewet et al.. Due to the paucity of knowledge regarding the dosage of clonidine for OCD, we administered a similar intial dose to what was used by Helewet study. page 3, paragraph 2

- ***6.It dose not determine the basic demographic and clinical characteristics for each group and the relation between this characteristics and the results.***

  Thank you for your recommendation. It has been added. Page 6

7.It does not determine generalizability of the trial findings.

- Thank you for your recommendation. The included patients met the inclusion criteria. Therefore, the current study has not been conducted on a particular group of patients and it can be generalized; however, we recommend further studies to apply these outcomes. Conclusion part, line 10-14

8.It does not determine trial limitation.

- Thank you for your recommendation.. Limitations part, page 8

Reviewer 2:

The authors evaluated the effect of clonidine on the treatment of patients with refractory OCD. It is interesting idea. However, I concerned about several issues of this paper.

Title

1) The title should be revised. According to the CONSORT recommendation, it is merit to note "randomized clinical trial" in the title.

- Thank you for your valuable notification. It has been added.

Abstract

2) State p values clearly.

- The p-values were clearly mentioned if applicable, but the last one which related to the final drug complications could not be presented clearly due to the diversity of complications.

3) State length of follow-up.

- Thank you for your recommendation. It has been done.. Abstract, methods, line 2-3

Introduction

4) Mention previous researches to resolve this problem.

- Thank you for your recommendation. It has been done. Introduction, page 2, paragraph 2, lines 3-7.

5) Please clarity of the objectives.

- Thank you for your recommendation. It has been done. Page 2, paragraph 3

6) State primary and secondary outcomes.

- Thank you for your recommendation. It has been done. Page 2, paragraph 3

Materials And Methods

7) How did authors select participants?

- Thank you for your recommendation. It has been done. Page 3, paragraph 3

8) What is definition of refractory cases?

- Thank you for your recommendation. It has been done. According to inclusion criteria, refractory OCD refers to a patients with severe OCD (above 16 score) based on Y-BOCS

questionnaire who has not responded for the period of 12 weeks treatment with maximal tolerable dose of SSRI or clomipramine. Page 2, paragraph 5

9) How did authors estimate enough sample size?

- Thank you for your recommendation. The formula and calculation has been added. Page 3, paragraph 2

10) How this research was performed blinded? The adverse effects of clonidine can confound with blindness.

- Thank you for your recommendation. The mentor and the psychologist were blinded to the treatment, while the resident responsible for the treatment was aware of the medications. Therefore, after the medication administration which was controlled by the resident, the patients were visited by the mentor and the questionnaires were completed by the psychologist. The administered medications were encoded as 1 or 2 on the top of the questionnaire. The drugs were delivered to the patients by the resident in blinded packages.

11) State the registry number of IRCT. This proposal was received the ethical approval at 2018/10/08. However, the authors recruited OCD participants from May 2016.

- Thank you for your recommendation. It has been added. Page 3, paragraph 1, lines 2-3

12) DSM-V-TR?

- Thank you for your recommendation. We administered DSM-5 which is the last promoted version by APA to diagnose psychiatric disorders.

13) The authors cited criterion of severity to an inappropriate reference (number 6).

- Thank you for your recommendation. The validate Persian version has been added.

14) How did authors conduct block randomization? State in detail.

- Thank you for your recommendation. The administered sampling method of blocking was in a way that an equaled number of patients in particular intervals were divided into 15 blocks each included 4 members. Each member of a block was provided with a number using Randomization crosstabs. Therefore, two of each block was allocated to the control and the two other ones to the case group.

15) Describe measurement tools.

- Thank you for your recommendation. It has been described in page 4, paragraph 1 and 2.

16) When was clonidine given?

- Thank you for your recommendation. The augmentation therapy was initiated as soon as the diagnosis of refractory OCD was made. Page 3, paragraph 7.

17) The authors explained that 1 mg/day clonidine is maximum dose of clonidine in the psychiatric disorders. However, Hewelett study showed that 1 mg/day clonidine is ineffective in patients with OCD.

- Thank you for your recommendation. As it is mentioned in the manuscript as well, due to the adverse effects of clonidine such as hypotension and drowsiness, the clonidine treatment was initiated by a half pill and then, gradually increased according to the tolerance of the patient or achieving the acceptable responses. Accordingly, the mentioned references have presented that the appropriate response was achieved in 2 microgram/kg.

18) How to check normal distribution in data?

- Thank you for your recommendation. The normality of data distribution in the Y-BOCS and CGI tests were assessed using Kolmogrov-Smirnov test. As all the P-values were greater than 0.05; therefore, the data were distributed normally. Page 4, Statistical analysis

19) Identify where Benferroni correction was used.

- Thank you for your recommendation. The mean number of four times assessment of CGI and Y-BOCS were compared using Benferroni test which revealed significant P-value of 0.001. It has been added. Page 7

Results

20) In the result part, the demographic characteristics of two groups should be noted.

- Thank you for your recommendation. It has been added. Page 6

21) The z score of different part of mapping before and after intervention, 95% confidence of difference and p value should be mentioned.

- Thank you for your recommendation. Considering the normal distribution of the variables, we applied repeated major ANOVA test and it seems that Z score is not required to compare the variables.

22) In total 1 out of 30 participants lost to follow-up in the case group due to adverse effects of clonidine. There is necessary to consider this case.

- Thank you for your recommendation. The patient who left the study complained from lightheadedness occurred because of bothering hypotension. Page 4, last paragraph

23) Draw consort flowchart.

- Thank you for your recommendation. Figure 1 has been added.

24) The statistical analyses are incorrect. How did the authors control covariates or confounders?

- Thank you for your recommendation. As the only controlled variables between the two groups were age and gender, the groups were similar and none of the assessed characteristics did

not play a confounding role. It is one of the limitations of the study that has been mentioned in the limitation section.

Discussion

25) Explain about possible mechanisms of clonidine effect on the OCD.

- Thank you for your recommendation. A paragraph about the possible mechanism of clonidine has been added. Discussion, paragraph 3.

26) It is better to say "This research showed the enough evidence to reject null hypothesis".

- Thank you for your recommendation. This sentence has been added to the conclusion part

27) State the strengths and limitations.

- Thank you for your recommendation. Limitation part has been added. The most strength of this study is its design which has been conducted in controlled randomized blind method.

References

28) There is only five references for the last 5 years.

- Thank you for your recommendation. More recent studies have been added.

Reviewer 3:

The study method is acceptable, by and large, although there are some issues about the sent manuscript which are listed below:

1. "psychological" should be replaced with "neuropsychiatric" in the first sentence of the abstract.

- Thank you for your recommendation. The term has been changed.

2. "YALE-BROWN OBSESSIVE COMPULSIVE SCALE (Y-BOCS)" should be used as usual capital name. As well as, duration of the trial should be mentioned in the abstract.

- Thank you for your recommendation. The recommended tips have been added to the method part.

3. One or two sentences about basic biological theory of the trial should be added to the abstract.

- Thank you for your recommendation. It has been added to abstract, forth sentence.

4. Mean difference of each group and mean scores before and after intervention should be mentioned in the abstract.

- Thank you for your recommendation. It has been added to abstract, results.

5. Type of the study should be mentioned in the title.

- Thank you for your recommendation. It has been added.

6. Biological theory of the trial as well as other etiological theories of the OCD such as glutamate, serotonin and neuroinflamation should be described in both introduction and discussion and findings of the current study should be compared with former studies.

- Thank you for your recommendation. he required information has been added. Page 1, the last paragraph and page 2, paragraph 1-4. In discussion part, page 8, paragraph 3

7. "The current study is a double-blinded randomized-clinical-trial conducted on 57 obsessive compulsive diseases based on Clinical Neuropsychiatry 2013" is not clear at all. What is Clinical Neuropsychiatry 2013?

- Thank you for your recommendation This sentence is not correct and has been removed from the study.

8. What does DSM-V-TR mean in the method?

- Thank you for your recommendation. This term was wrong. The corrected term is DSM-V.

9. Dosage of clonidine seems to be higher than usual. The authors should explain how many pills were prescribed daily? How was Blood Pressure assessment of the participants?

- Thank you for your recommendation. According to the Eric et al. study, clonidine administration was effective in 2 microgram/kg doses. Therefore, we initiated clonidine therapy by half a pill (1 mg) daily dose and then, increased the dosage weekly until achieving appropriate responses or the patient presented adverse effects. The blood pressure was measured at baseline and then, every four weeks.

10. Method should be rewritten as a structured part.

- Thank you for your recommendation The method part has been corrected and rewritten in a structured part.

11. IRB code and IRCT code should be mentioned.

- Thank you for your recommendation. It has been added to the method part.

12. "From the rater group..." from the text. What does rater group mean?

- Thank you for your recommendation. The word rater was wrong and latter is correct. The word has been corrected. Results, paragraph 1, line 4

13. Based on table-1, seems that improvement among clonidine group is higher than placebo group, significantly. If so, the trial should be reported as positive finding in all part of the manuscript, more specifically abstract.

- Thank you for your recommendation. Clonidine treatment revealed superior outcomes in some intervals but in general, the comparison of the two groups revealed insignificant difference. Based on table 1, CGI comparison revealed P-value of 0.22 and Y-BOCS revealed P-value of 0.06.

14. Higher side effects in clonidine group should be emphasized in the abstract as well.

- Thank you for your recommendation It has been added to the result part of the abstract.

15. Previous studies should be explained more in the discussion to be compared.

- Thank you for your recommendation. The discussion part has been more exntensively explained. Page8, paragraph 3 and 5 and page 9, paragraph 2.

2 Revision 1

1 comment · 30 Apr 2021

Editor-in-Chief

MINOR REVISION 30 Apr 2021

Thank you for your recent revisions.

Please write "DSM-5" instead of "DSM-V".
Besides, revise the references according to the guidelines of the journal.
- Please use the abbreviated names of the journals according to the MEDLINE database. You also may find abbreviations on the Wikipedia website.
- You should mention the language of non-English (e.g., Persian) references in parentheses too.
- Add the DOI of each article at the end of its reference.
- At the end of the references that are books, in addition to the name of the publisher, write the city of publication.
- Correct the author's name in reference 17.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Please write "DSM-5" instead of "DSM-V".

Thank you for your comment. The term DSM-V change to DSM-5.

Besides, revise the references according to the guidelines of the journal.
- Please use abbreviated name of the journals according to MEDLINE database. You also may find abbreviations on the Wikipedia website.

Thank you for your comment.Thementioned changes have been done.
- You should mention the language of non-English (e.g. Persian) references in parenthesis too.

Thank you for your comment.Thementioned changes have been done.
- Add the DOI of all the articles at the end of them.

Thank you for your comment.Thementioned changes have been done.
- At the end of the references that are books, in addition to the name of the publisher, write the city of the place of publication.

Thank you for your comment.Thementioned changes have been done.
- Correct the author's name of reference 17.

Thank you for your comment.Thementioned changes have been done.

3 Revision 2

5 comments · 21 May 2021 – 5 Jun 2021

Mohammadreza Shalbafan Reviewer — ACCEPT — 21 May 2021

Thanks for sending the manuscript. It seems to me that the required revisions were performed. It's acceptable.

Referee 1 Reviewer — ACCEPT — 29 May 2021

I have no comment.

Referee 2 Reviewer — REJECT — 31 May 2021

Although I did not find any response by the authors to the reviewers' comments and the changed phrases were not highlighted, I re-evaluated the manuscript. Unfortunately, there are many comments that the authors did not consider.

Associate Editor — MINOR REVISION — 1 Jun 2021

One of the peer reviewers has rejected the article. The reason for this rejection was the failure to highlight the changes and to make many of the requested revisions.

Dear authors!
Please reconsider the reviewers' comments on the previous version and highlight the changes in the article, and then resubmit it again.
best

Editor-in-Chief — MINOR REVISION — 5 Jun 2021

Thank you for your recent revisions.
Your paper has now been evaluated again. According to the reviewers' and associate editor's comments, it needs some more revisions. Please make your revisions according to these comments. I would appreciate it if you could make the revisions as soon as possible using the track changes mode in MS Word and colored text.

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer 1:
Thanks for sending the manuscript. It seems to me that the required revisions were performed. It`s acceptable.

- *Thank you for your favor. Best regards.*

Reviewer 2:
I have no comment

- *Thank you for your favor. Best regards.*

Reviewer 3:
Although I did not find any response to reviewers' comments by the authors and the changed phrases did not highlighted, I re-evaluated the manuscript again. Unfortunately, there are many comments that the authors did not consider them.

- Thank you for your comment. Your requested corrections are colored in green.

Reviewer 3:

The study method is acceptable, by and large, although there are some issues about the sent manuscript which are listed below:

1. "psychological" should be replaced with "neuropsychiatric" in the first sentence of the abstract.

- Thank you for your recommendation. The term has been changed.

2. "YALE-BROWN OBSESSIVE COMPULSIVE SCALE (Y-BOCS)" should be used as usual capital name. As well as, duration of the trial should be mentioned in the abstract.

- Thank you for your recommendation. The recommended tips have been added to the method part.

3. One or two sentences about basic biological theory of the trial should be added to the abstract.

- Thank you for your recommendation. It has been added to abstract, forth sentence.

4. Mean difference of each group and mean scores before and after intervention should be mentioned in the abstract.

- Thank you for your recommendation. It has been added to abstract, results.

5. Type of the study should be mentioned in the title.

- Thank you for your recommendation. It has been added.

6. Biological theory of the trial as well as other etiological theories of the OCD such as glutamate, serotonin and neuroinflamation should be described in both introduction and discussion and findings of the current study should be compared with former studies.

- Thank you for your recommendation. he required information has been added. Page 1, the last paragraph and page 2, paragraph 1-4. In discussion part, page 8, paragraph 3

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- Thank you for your recommendation This sentence is not correct and has been removed from the study.

8. What does DSM-V-TR mean in the method?

- Thank you for your recommendation. This term was wrong. The corrected term is DSM-V.

9. Dosage of clonidine seems to be higher than usual. The authors should explain how many pills were prescribed daily? How was Blood Pressure assessment of the participants?

- Thank you for your recommendation. According to the Eric et al. study, clonidine administration was effective in 2 microgram/kg doses. Therefore, we initiated clonidine therapy by half a pill (1 mg) daily dose and then, increased the dosage weekly until achieving appropriate responses or the patient presented adverse effects. The blood pressure was measured at baseline and then, every four weeks.

10. Method should be rewritten as a structured part.

- Thank you for your recommendation The method part has been corrected and rewritten in a structured part.

11. IRB code and IRCT code should be mentioned.

- Thank you for your recommendation. It has been added to the method part. Page 3, paragraph 5.

12. "From the rater group..." from the text. What does rater group mean?

- Thank you for your recommendation. The word rater was wrong and latter is correct. The word has been corrected. Results, paragraph 1, line 4

13. Based on table-1, seems that improvement among clonidine group is higher than placebo group, significantly. If so, the trial should be reported as positive finding in all part of the manuscript, more specifically abstract.

- Thank you for your recommendation. Clonidine treatment revealed superior outcomes in some intervals but in general, the comparison of the two groups revealed insignificant difference. Based on table 1, CGI comparison revealed P-value of 0.22 and Y-BOCS revealed P-value of 0.06.

14. Higher side effects in clonidine group should be emphasized in the abstract as well.

- Thank you for your recommendation It has been added to the result part of the abstract.

15. Previous studies should be explained more in the discussion to be compared.

- Thank you for your recommendation. The discussion part has been more exntensively explained. The paragraphs in green color
-

4 Revision 3

2 comments · 9 Jul 2021 – 17 Jul 2021

Associate Editor

ACCEPT 9 Jul 2021

Dear Editor
The necessary revisions that were mentioned by the reviewers were all made and highlighted. In my opinion, this article can be considered for publication. The only point that should be noted is that I did not find the ethical approval code of Isfahan University in the text, although the need to mention this code has recently been emphasized. Of course, the IRCT code was available.
Thanks

Editor-in-Chief

ACCEPT 17 Jul 2021

We have completed our review of your manuscript and are pleased to inform you that it is being considered for publication in the IJPBS. Note that the publication of your article will only be finalized with your cooperation in the editorial process.
Thank you for your fine contribution. On behalf of the Editors of IJPBS, we look forward to your continued contributions to the Journal.