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OPEN PEER REVIEW

Efficacy of Donepezil in Improving Cognitive Impairment Induced by Electroconvulsive Therapy in Patients with Mood Disorders: A Randomized, Double-blind, Placebo-Controlled 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.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

4 comments · 24 Oct 2020 – 1 Jan 2021

Referee 1 Reviewer

MAJOR REVISION 24 Oct 2020

Thanks for the submission:
Considering that the severity of cognitive impairment in depressive disorders varies, how could you deal with this confounding factor?
Many mood disorders could be the result of substance use or withdrawal, but there is no mention of substance use in the exclusion criteria.
Why were only psychiatric interviews used to diagnose depressive disorder? Is there any reason for not using a questionnaire?
How did you deal with other comorbidities that lead to cognitive impairment (such as associated anxiety disorders)?
In the study methods, there is no mention of the intensity of ECT. Considering that the seizure threshold differs between participants, could the intensity of ECT have affected patients' cognition?
The study did not consider the participants' medical history, although many psychotropic drugs and even other drugs could affect patients' cognition.

Referee 2 Reviewer

MINOR REVISION 1 Jan 2021

Please see my review in the attached file.

Associate Editor

MINOR REVISION 1 Jan 2021

This is with further reference to your paper submitted for possible publication in IJPBS.
Your paper has been carefully reviewed, and it is suggested that the manuscript requires considerable revision and should be modified according to the reviewers' comments, which are appended below.

Editor-in-Chief

MINOR REVISION 1 Jan 2021

Your paper has been evaluated by external peer reviewers. Please make your revisions according to the reviewers' 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.

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.

Dear editor

Thank you for reviewing our manuscript. We have provided the reviewers' comments below:

Reviewer 1:

With consideration of the severity of cognitive impairment in depressive disorders is not equal, how could you deal with this confounding factor?

As shown in Table 2, the severity of cognitive deficits was assessed and compared for all patients at baseline and over time. There were no significant differences in the cognitive deficits in the intervention and placebo groups before the study. We aimed to evaluate the Donepezil efficacy on cognitive impairment caused by electroconvulsive therapy (ECT). We compared the changes in mean +- SD over time. Moreover because sampling were randomly, patients with different depression severity were present in both groups.

Many mood disorders could be result of substances use or withdrawal, but there is no mention of substance use in the exclusion criteria

None of the patients had substance induced mood disorder. We mentioned it in exclusion criteria.

Why the criteria for diagnosing depressive disorder were only psychiatric interviews? Is that any reason for not using of questionnaire?

The patient evaluated for psychiatric disorder according to SCID-5 for diagnosing of MDD, Bipolar disorder and other comorbidities. As we know, diagnosis in psychiatry is made based on DSM-5 criteria. Questionnaires are auxiliary tool that mostly used to evaluate the course of treatment. Questionnaires cannot be a substitute for psychiatric interviewing in diagnosis.

How did you deal with other comorbidity that leads to cognitive impairment (such as associated anxiety disorders)?

Most of mood disorder patients have anxiety. Patients were randomly assigned in each group. So it seems groups were similar in this respect.

On the study method there is no mention to the intensity of ECT. Considering that the threshold of seizure is different between participants, could the intensity of ECT was an effective factor in patients' cognition?

As presented in the table 1, there was no difference between stimulus energy between the groups. The mean +_ SD in the intervention group was 34.7±7.3. On average there wasn't a significant difference between patients in the intensity of ECT. Moreover we compare the mean during the study.

The study did not consider the participants' medical history. While many of psychotropic drugs and even other drug could be effect on patients' cognition.

The patients were evaluated for psychiatric disorder according to SCID-5 for diagnosing MDD, Bipolar disorder, and other comorbidities. The patients' medications were not the same. In many other studies that evaluate a drug efficacy on cognitive impairment caused by ECT the medications were not the same. However, an SSRI or SNRI has been prescribed for most MDD patients. An antipsychotic has been administered for most bipolar patients. As presented in table 1, most patients were in their fourth or fifth decade of life. None of them have an uncontrolled physical illness. As we said in the method section, All participants underwent a physical examination.

Reviewer 2:

We corrected the manuscript concerning all comments.

Best regards

2 Revision 1

2 comments · 21 Jan 2021 – 21 Jan 2021

Associate Editor

MAJOR REVISION 21 Jan 2021

Thank you for making the revisions. Most answers are acceptable. But as you said in the answers, "the patients' medications were not the same", and "none of them had an uncontrolled physical illness". It is recommended to mention the non-uniformity of drugs as one of the limitations of the study at the end of the discussion. Also, given that the patients may have had a controlled physical illness that affected their cognitive functions, if they have been evaluated and matched in terms of controlled physical illness, this should be explicitly mentioned. But if this has not been done, this should be mentioned as one of the limitations of the study. Please pay attention to her review and send the appropriate answers and corrections/revisions.

Editor-in-Chief

MAJOR REVISION 21 Jan 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.

Besides, please pay attention to the word count limitation.

Word count limits are declared at 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 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.

Dear editor

Thank you for reviewing our manuscript. We have provided the reviewer' s comments below:

Please give reference for this sentence

The Kaplan and Sadock's Synopsis of psychiatry has been used to write the first two sentences.

Please give reference for this sentence

The authors wrote this sentences according to literature review. As mentioned in the next sentences in the manuscript, there were just three study that evaluate donepezil for ECT-induced cognitive impairments.

It would be helpful to briefly explain about contradictory results between studies in this topic.

We explain previous studies in more detail.

Why didn't laboratory assessment during or at the end of the study?

All admitted patients are evaluating about some laboratory tests routinely in psychiatric wards for detecting any other medical condition. Regarding to evidence donepezil has no significant effect on lab tests.

Sample size

We explained it in more detail.

Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions?

We explain it in more detail.

Were patient allowed to receive other drug?

You know patients with the mental disorder **need** to receive some other drugs during the ECT. It was not ethical to discontinue them. So other psychiatric medications such as SSRI/SNRI/Antipsychotics continued. It is **not possible** to discontinue all of them. Moreover, it is not seems the type of medication is a significant confounder. There is not a significant difference between cognitive side effects of SSRIs and or SNRIs in MDD patients and also atypical antipsychotics in BID patients.

It is better to delete these sentences because they are given in Table 1.

We deleted them.

We rewrite discussion part. Table 2 was changed due to the comments.

We corrected the manuscript concerning all other comments.

Associate Editor*:*

We evaluated the patients concerning any uncontrolled medical illness. So we mentioned it as an exclusion criterion.

The non-uniformity of drugs had been mentioned as a limitation in the discussion part of the manuscript previously.

Best regards

3 Revision 2

3 comments · 6 Mar 2021 – 29 Mar 2021

Referee 3 Reviewer

MAJOR REVISION 6 Mar 2021

Comments are in the attachment

Associate Editor

MAJOR REVISION 29 Mar 2021

Thank you for your recent revisions.
Your paper has now been evaluated again by the external peer reviewer. Unfortunately, you have not made all of the requested revisions, nor have you responded to all of the reviewers' comments. Please revise your paper according to these comments. I would appreciate it if you could make the revisions as soon as possible using Track Changes in MS Word and colored text.

Editor-in-Chief

MAJOR REVISION 29 Mar 2021

Thank you for your recent revisions.
Your paper has now been evaluated again. According to the reviewer's 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.

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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.

Dear editor

Thank you for reviewing our manuscript. We have provided the reviewer's comments below.

We gave references for sentences in introduction. We also used new reference to re-write .1
.introduction and discussion parts

We explained how to minimize the possible effect of drugs on the study results in the .2
.limitation section

Table 2 had been changed due to comments. We think it might be dissembled during pdf .3
.production on the journal page. However, we corrected it again

.We deleted mentioned sentences .4

We briefly stated the reason or reasons for the conflicting results obtained from the studies in .5
.objective part

6. SCID-5 is a correct abbreviation. You can see this term on the APA or Cambridge website. The links are below:

https://www.appi.org/products/structured-clinical-interview-for-dsm-5-scid-5

https://www.columbiapsychiatry.org/research/research-labs/diagnostic-and-assessment-lab/structured-clinical-interview-dsm-disorders-11

7. We rewrote result. Discussion and statistical analysis changed according to the comments.

4 Revision 3

3 comments · 24 Apr 2021 – 29 Apr 2021

Referee 3 Reviewer

MAJOR REVISION 24 Apr 2021

Please see the attachment.

Associate Editor

MAJOR REVISION 29 Apr 2021

Thank you for your recent revisions.
Your paper has now been evaluated again by the external peer reviewer. Unfortunately, you have not completed all of the requested revisions, nor have you responded to all of the reviewer's comments. Please revise your paper according to those 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.

Editor-in-Chief

MAJOR REVISION 29 Apr 2021

Thank you for your recent revisions.
Your paper has now been evaluated again. According to the reviewer's 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.

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Revision 4

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.

Dear editor

Thank you for reviewing our manuscript. We have provided the reviewer's comments below.

We do not know what you mean by this sentence "please indicate the criteria for ECT"?

Did you mean we explain what the indication of ECT in psychiatry is?

Psychiatrists use ECT for different indications. For example, treatment-resistant or severe episodes, severe aggression or agitation, suicidal thoughts, etc. It depends on the psychiatrist's clinical judgment.

We rewrite paragraph two of statistical analysis regarding the reviewer's comment.

Here is a major problem that we have, and a satisfactory consideration and discussion of this issue is a requirement for further consideration of the paper. The present study indicated that "donepezil co-administration with ECT may be useful in improving the ECT induced cognitive disturbances". The question is: you did not assess the severity of the mood symptoms at baseline and during the study. There is a possibility that improvement of mood disorders led to the clinical picture suggested as improvement of cognitive status.

This study was a randomized placebo-control clinical trial. If improvement of mood disorders led to the clinical picture it is correct for both of the groups. As you in table 2 and figure 2, cognitive status improved in groups at the study endpoint. However, the improvement of cognitive performance in the donepezil group was significantly superior to the placebo group. Moreover, randomization would have assisted balanced the effect of different severity between study groups. Also, ECT often is used for the treatment of severe episodes.

What specific SSRI, SNRI or atypical antipsychotic drugs were the patients taking?

As we mentioned in the last paragraph of the discussion, we could not homogenize the participants in terms of drugs, the number of episodes, and the duration of the disease.

However, we believed randomization would have assisted balanced the effect of them between study groups.

There were just three studies that investigate the efficacy of donepezil for ECT-induced cognitive impairment. In our study, the number of the participant was more than them. Also, we homogenized psychiatric diagnoses. In other studies,

patients with different psychiatric diagnoses were enrolled. You know it is impossible to consider everything identical in groups. Randomization may be helpful to balance this problem.

Table 2 can be combined with Table 2.

???????????

Did you mean table 2 can be combined with table 1? We prefer to use two tables. It seems it could be difficult and confusing to understand if all of the data is provided in just one table.

We provided all other comments.

Best regards

5 Revision 4

1 comment · 6 May 2021

Editor-in-Chief

MINOR REVISION 6 May 2021

Thank you for your recent revisions.
Your paper has now been evaluated again. Unfortunately, you have not completed all of the requested revisions, nor have you responded to all of the reviewer's comments. Please revise your paper according to those comments. I would appreciate your making the revisions as soon as possible using the track changes mode in MS Word and colored text.
1- Here is a major problem that we have, and a satisfactory consideration and discussion of this issue is a requirement for further consideration of the paper. The present study indicated that "donepezil co-administration with ECT may be useful in improving the ECT induced cognitive disturbances". The issue is that you did not assess the severity of the mood symptoms at baseline and during the study. There is a possibility that improvement in mood disorders led to the clinical picture described as improvement in cognitive status.
2- Please provide data on the number of episodes, duration of disease, and baseline MMSE, total ACE-R, and ACE-R subscale scores for patients in each group in table 1.
3- What specific SSRI, SNRI, or atypical antipsychotic drugs were the patients taking? Enter this information in table 1.

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Revision 5

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.

Dear editor

Thank you for reviewing our manuscript. We have provided the reviewer's comments below.

1- Here is a major problem that we have, and a satisfactory consideration and discussion of this issue is a requirement for further consideration of the paper. The present study indicated that "donepezil co-administration with ECT may be useful in improving the ECT induced cognitive disturbances". The question is: you did not assess the severity of the mood symptoms at baseline and during the study. There is a possibility that improvement of mood disorders led to the clinical picture suggested as improvement of cognitive status.

As we explained in the previous revisions, this was a randomized placebo-controlled study. Therefore, if improvement of mood disorders led to the clinical picture, it is correct for both of the groups, not just the donepezil group. You know at the end of the study cognitive status improved in both groups. But the improvement was significantly higher in the donepezil group. So it seems that donepezil is useful in improving cognitive status. It is obvious that ECT improves mood symptoms but, this is true for both groups, not just for one of them. Moreover, ECT is often used for a **severe and/or treatment-resistant mood disorder.** Therefore although we didn't assess the severity using a questionnaire it didn't seem severity was significantly different between the groups. Moreover, the baseline cognitive status of the groups was not significantly different. It might affect baseline cognitive status if disease severity were significantly different in the groups. A psychiatrist decides to finish the ECT as soon as the exacerbation episode of mood disorder subsides. Subside is achieved after 8 ECT sessions for both groups. It seems that symptom severity would not be significantly different at the study endpoint. Also, this was a randomized clinical trial. If there were a significant difference between the groups in terms of severity, randomization would have assisted balanced this effect.

2-Please provide data on number of episodes, duration of disease of patients and baseline MMSE and total ACE-R and its subscales scores in each group in table 1.

As we explained in the previous revisions, we could not homogenize the participants in terms of the number of episodes, and the duration of the disease. However, we believed randomization would have assisted balanced the effect of them between the study groups. We had explained this limitation in the discussion. We had provided baseline MMSE and total ACE-R and its subscales scores in each group in table 2. However, we presented them in Table 1 too.

3-What specific SSRI,SNRI or atypical antipsychotic drugs were the patients taking? Enter in table 1.

As we explained in the previous revisions, we could not homogenize the participants in terms of their drugs. They were prescribed an SSRI/SNRI (fluoxetine, sertraline, citalopram, fluvoxamine, venlafaxine, etc.) for MDD. Atypical antipsychotics (aripiprazole, olanzapine, risperidone, and quetiapine) were prescribed in B1D patients. You know SSRI/SNRIs have not any significant different effect on cognitive status. This is true for atypical antipsychotics too. However, we believed randomization would have assisted balanced the possible effect of different drugs between the study groups. We had explained this limitation in the discussion.

Best regards

6 Revision 5

2 comments · 28 May 2021 – 17 Jul 2021

Associate Editor

ACCEPT 28 May 2021

Corrections and responses submitted are acceptable.

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 be finalized only 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.