OPEN PEER REVIEW

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As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:

Peer Review

Journal of Comprehensive Pediatrics
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Peer Review Report for "Analysis of Association Between the Effects of Methylphenidate and *DRD4* Gene Polymorphisms in Patients with Attention Deficit Hyperactivity Disorder"

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Review Timeline:

Submit Date:	27 Oct 2020
Revised Date:	10 Oct 2021
Accepted Date:	19 Oct 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE : Reviewer

20 Aug 2021

Thank you for presenting this manuscript. But I have many questions about this presentation:

Abstract:
We are not allowed to use any abbreviation word without definition for the first time: ADHD, ...and so on
In title was seen investigation of “side effect” but in object “effect”.

In methods; when? Where? Statistical analysis methods?. Pl explains briefly.

Introduction:

Paragraph 5 and 5 had repetitive sentences. Pl omits one of them.

I ask you the critical question: Many studies have been done in this regard. Why the authors decided to conduct this study again? Which new question does the findings of this study answer? What is novelty of this study?

Methods:

ADHD children aged 5-18 years!! Children were mentioned in the title, but in the text the age of subjects was 5- 18 years old. It is suggested that the study groups should be more limited to only child or the word “children should be omitted from the title. Meanwhile, the first scenario is better done in term of methodology.

Paragraph 2 need paraphrase, totally. The authors said: “The sampling was availably done based on the inclusion and exclusion criteria”. The eligibility of subject is different from allocation. At first, sampling methods should be mentioned clearly and then in base of the inclusion and exclusion criteria allocation should be done to complete the allocation. So What was sampling methods?

How did you calculate the sample size? Which formula did you use?

Inclusion and exclusion criteria were incomplete. Pl defines precisely and clearly. What no assessed for eligibility? And then what no was allocated? Did you Lost to follow-up?

Inclusions and exclusions criteria must be mention to first paragraph then after, eligible and allocated participants were noted (with number, exact and clearly).

What was mean of parental satisfaction?! Pl changes to consent.

“Response to treatment was defined as at the least 50% decrease in Conners score”need references.

Generic name, dose, and administration type are required for the used medications.

Statistical methods and general computer programs (software) must be mentioned.

The used Info system should be clearly noted.

Results:

One of your exclusion criteria was “mainpsychiatric simultaneity disorder” but in table 2 was shown multiple mainpsychiatric disorder such as: Psychiatric comorbidity 12 (% 8.6), Major depressive disorder 1 (% 0.7), Obsessive compulsive disorder 1 (0.7), Tic disorder 2(%1.4), Anxiety disorder 3 (% 2.1) and Oppositional defiant disorder 5 (%3.6)!!!!? pl explain it precisely and clearly. Are not these con-founders factors?

Total studied subjects were 122 but male/female was 118/22!!!?118+22= 140!!

All number and frequency percent in tables (1,2 and 3) must be re-checked up, precisely.

There are many confounding factors in the studies about treatment response (such as ages, Psychiatric co-morbidity and many others variables that may influence the rate and amount of response during treatment. How did you include the confounding factors in the results? Clearly define all potential confounders and effect

modifiers. Give diagnostic criteria, if applicable.
Describe statistical methods, used to control for confounding.
Control of confounders is an important point in this study.
Describe any sensitivity analyses.
Did you have missing data?
Please explain confounder and test to confounder-adjusted.
Minimize and control of confounders should be performed in three ways: 1- restriction the study population, 2- matching the two comparison groups and 3- stratifications of pooled data, but you did not.
You used wide ages range, sex disproportion, no matching seen between two groups (response and non- response subjects), no stratifications of pooled data for each groups and number disproportion between two groups. Several methodological mistakes further hamper the overall quality of the manuscript and the authors may consider reviewing checklist in order to improve their manuscript.
Legends and title of figures must be placed at the bottom of the figure (no in top).

Discussion:
Paragraphs 1 were repetitive (it has noticed in background) and not suitable in this section.
In the discussion part you should write the main(s) finding(s) and specially (novelty) at first and then allude to other studies (Paragraph 2 & 6).
It concentrates on the new and important aspects of the study and the achieve conclusions. Discussion should emphasize on the present findings and the variations or similarities with other related studies.
Limitation and recommendation should be mentioned in the last paragraph of discussion and in last paragraph any gap, question, hypothesis or comment should be declared (conclusion).
Meanwhile, the clinical statement of study should be defined precisely and clear.

References:
References did not arrange according to the rules of the journal (no APA).
Most of them were so old. The most of references were too old (before 2010, almost before 2005). There have been only a few references from 2010 (2 references 2010 & 1 ref 2015). References need renewal.
Thank you

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Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reply to Reviewers

Here is the reply to all reviewers' point by point:

Abstract

Q:We are not allowed to use any abbreviation word without definition for the first time: ADHD, …and so on
R: The title was changed as suggested by reviewer.

Q: In title was seen investigation of “side effect” but in object “effect”.
R: "Side effect" was changed to "effect" in the title.

Q: In methods; when? Where? Statistical analysis methods?. PI explains briefly.
R: Some modifications were made in abstract sections, such as, not using abbreviation, mentioning more details in method section about statistics, changing side effects to effects and using patients instead of children.

Introduction:
Q:Paragraph 5 and 5 had repetitive sentences. PI omits one of them.
R: In introduction, pharagraph5 was altered according to reviewer's comment.

Q: I ask you the critical question: Many studies have been done in this regard. Why the authors decided to conduct this study again? Which new question does the findings of this study answer? What is novelty of this study?
R: At the final part of introduction, the aim and objectives of this study was stated more clearly as it was suggested. The novelty of this study was that it was done for the first time in our ADHD patients.

Methods:
Q: ADHD children aged 5-18 years!! Children were mentioned in the title, but in the text the age of subjects was 5- 18 years old. It is suggested that the study groups should be more limited to only child or the word “children should be omitted from the title. Meanwhile, the first scenario is better done in term of methodology.
R: children was changed to patients instead throughout the manuscript. Therefore the world children was also changed in the title as well.

Q:Paragraph 2 need paraphrase, totally. The authors said: “The sampling was availably done based on the inclusion and exclusion criteria”. The eligibility of subject is different from allocation. At first, sampling methods should be mentioned clearly and then in base of the inclusion and exclusion criteria allocation should be done to complete the allocation. So What was sampling methods?

How did you calculate the sample size? Which formula did you use?
Inclusion and exclusion criteria were incomplete. PI defines precisely and clearly. What no assessed for eligibility? And then what no was allocated? Did you Lost to follow-up?
Inclusions and exclusions criteria must be mention to first paragraph then after, eligible and allocated participants were noted (with number, exact and clearly). What was mean of parental satisfaction?! PI changes to consent.
“Response to treatment was defined as at the least 50% decrease in Conners score”need references.
Generic name, dose, and administration type are required for the used medications.
Statistical methods and general computer programs (software) must be mentioned.
The used Info system should be clearly noted.

R: In methodology section, all the comments were suggested by reviewer was corrected. Inclusion and exclusion criteria were explained more clearly. Just to explain further, this descriptive-analytical study was performed on ADHD patients, aged 5-18 years, in Tabriz-Iran during 2016, who referred to child and adolescent psychiatry clinic in this city for receiving psychiatric services and needed drug treatment.
In the last part of method, reference was added to the response to treatment. Generic name, dose, and administration type were also added for the used medication.. Statistical method used is also explained.

Results:
Q: One of your exclusion criteria was “main psychiatric simultaneity disorder” but in table 2 was shown multiple main psychiatric disorder such as: Psychiatric comorbidity 12 (% 8.6), Major depressive disorder 1 (% 0.7), Obsessive compulsive disorder 1 (0.7), Tic disorder 2(%1.4), Anxiety disorder 3 (% 2.1) and Oppositional defiant disorder 5 (%3.6)!!!!? pl explain it precisely and clearly. Are not these con-founders factors?

R: As it was explained in exclusion criteria, patients with main psychiatric simultaneity was excluded from this study. Therefore, from 140 patients assessed, only 122 of them fulfilled the criteria. These psychiatric disorders were explained in the table (Major depressive disorder 1 (% 0.7), Obsessive compulsive disorder 1 (0.7), Tic disorder 2(%1.4), Anxiety disorder 3 (% 2.1) and Oppositional defiant disorder 5 (%3.6)).

Q: Total studied subjects were 122 but male/female was 118/22!!!?118+22= 140!!
R: This number is a total no. of patients examined but only 122 was passes the criteria.

Q:All number and frequency percent in tables (1,2 and 3) must be re-checked up, precisely.
R: these were double checked again as it was suggested.

Q: There are many confounding factors in the studies about treatment response

(such as ages, Psychiatric co-morbidity and many others variables that may influence the rate and amount of response during treatment. How did you include the confounding factors in the results? Clearly define all potential confounders and effect modifiers. Give diagnostic criteria, if applicable.
Describe statistical methods, used to control for confounding.
Control of confounders is an important point in this study.
Describe any sensitivity analyses.
Did you have missing data?
Please explain confounder and test to confounder-adjusted.
Minimize and control of confounders should be performed in three ways: 1- restriction the study population, 2- matching the two comparison groups and 3- stratifications of pooled data, but you did not.
R: In this genetic study, this does not apply. The aim of this study was to study the DRD4 mutation in ADHD patients who showed resistance to Retalin treatment and we achieved that by carry out the standard molecular protocol in our patients. Obviously, most reviewed papers in this regard showed similar methodology.

Q: You used wide ages range, sex disproportion, no matching seen between two groups (response and non- response subjects), no stratifications of pooled data for each groups and number disproportion between two groups. Several methodological mistakes further hamper the overall quality of the manuscript and the authors may consider reviewing checklist in order to improve their manuscript.
R: In this type of study it is not crucial to match the groups like psychological studies as it is the genetic variation that we were after not behavioral study. This gene is not on sex chromosomes so sex of patients does not matter in this regard. Depends on the gene and the location of the polymorphism, we set the limitations. In the results section, the statistical method used is according to genetic studies. All similar studies need to use the similar method to see the significance of genetic polymorphisms amongst their study group. However, the reviewer's suggestions about titles of the figures and usage of more details were taken into account and changed and highlighted for your attention. This study is designed to show the relevance of DRD4 polymorphism and resistance to Ritalin treatment in patients. So it not an epidemiological study to show the sex dispersion or age relevance as the number of patents for such a study is low and conclusion drawn for this cannot be consistent, however further studies would accomplish such a findings by using larger groups of patients.

Q: Legends and title of figures must be placed at the bottom of the figure (no in top).
R: This was altered as it was suggested.

Discussion:

Q: Paragraphs 1 were repetitive (it has noticed in background) and not suitable in this section.
R: This was altered as it was suggested.

Q: In the discussion part you should write the main(s) finding(s) and specially (novelty) at first and then allude to other studies (Paragraph 2 & 6).
R: We explained our data and findings in the first part of the discussion as it was suggested.
Q: Discussion should emphasize on the present findings and the variations or similarities with other related studies.
R: we have tried to use the available data in this regard, however, we have included more up to date studies as much as possible as it was suggested.

Q: Limitation and recommendation should be mentioned in the last paragraph of discussion and in last paragraph any gap, question, hypothesis or comment should be declared (conclusion).
Meanwhile, the clinical statement of study should be defined precisely and clear.
R: In discussion part, all the comments made by reviewer was alerted and highlighted.

References:

Q: References did not arrange according to the rules of the journal (no APA).
R: References were changed to APA format.

Q: Most of them were so old. The most of references were too old (before 2010, almost before 2005). There have been only a few references from 2010 (2 references 2010 & 1 ref 2015). References need renewal.
R: All the correction were made on reference section and they were corrected thoroughly.

OPEN PEER REVIEW

Revision (1)

REFEREE : Reviewer

19 Oct 2021

I totally appreciate the efforts that have been done by the authors in conducting this interesting study .
the most points mentioned have been changed by authors. The manuscript is now acceptable and printable.
thank you