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OPEN PEER REVIEW

Atomoxetine Versus Combination of Methylphenidate Plus Fluoxetine for Management of Anxiety Disorders in ADHD Children: 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

4 comments · 6 Feb 2023 – 6 Mar 2023

Referee 1 Reviewer

MINOR REVISION 6 Feb 2023

The purpose of this randomized controlled study is to assess the effectiveness of treating children with ADHD and anxiety by comparing a combination of methylphenidate (MPH) and fluoxetine (FLX) with atomoxetine (ATX). In 2020-21, 76 children with concomitant ADHD and anxiety disorder were enrolled. ATX alone was as effective as MPH + FLX in treating anxiety problems in children with ADHD, according to the authors; thus, ATX should be preferred over other daily drugs.

1. How was the sample size for this trial determined? Did you calculate the power of this measure?
2. According to the authors, "The mean age of the studied population was 9.26±1.92 years old among which 46 (50%) ones were males". Do 46 patients correspond to 50% of the participants?
3. The results section is very brief and needs to provide more explanations and details.

Referee 2 Reviewer

MINOR REVISION 25 Feb 2023

This study needs minor revision.

Associate Editor

MAJOR REVISION 4 Mar 2023

More explanation of the study method is needed. However, the discussion and conclusion sections need more elaboration.

Editor-in-Chief

MAJOR REVISION 6 Mar 2023

Thank you for submitting your manuscript for consideration for publication in the Iranian Journal of Psychiatry and Behavioral Sciences. Your paper has been evaluated by external peer reviewers. Please revise your manuscript according to the reviewers' comments.

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 specified 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. Revisions must be highlighted in the full manuscript file.

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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.

Reviewer 1:

The purpose of this randomized controlled study is to assess the effectiveness of treating children with ADHD and anxiety with a combination of methylphenidate (MPH) and fluoxetine (FLX) with atomoxetine (ATX). In 2020-21, 76 children with concomitant ADHD and anxiety disorder were employed. ATX alone was equally effective as MPH + FLX in treating anxiety problems in children with ADHD, according to the authors; thus, ATX should be preferred over other daily drugs.

1. **How the sample size for this trial was determined? Did you calculate the power of this measure?**

   Dear reviewer. Thank you for your comment. Actually, the primary measured sample population for each group accounted for 50 cases, but by the emergence of COVID-19 in 2019, closing of the school and reluctance of the ADHD patients to refer for treatment, we could not gather the required cases and due to the limitations of specialty course in Iran for graduation, the type 1 fault was changed in order to decrease the study population to the gathered one (38 ones in each group).

   The formula is as following:

$$N=\frac{¿2S^2(Z1+Z2)^2}{D^2}$$

Z1: 95% confidence interval= 1.96,

Z2: 80% power coefficient= 0.84,

S: One-sixth of the Conners score range of variation= 1/6* 144.6= 24

D: Minimum mean difference of Conners score between two groups= 14

The calculation with these numbers accounted for 46 patients in each group that by considering 10% withdrawal, the number of 50 patients was considered. Nevertheless, due to the problems after COVID-19 outbreak, the 10% withdrawal was increased to 25% and the measurements decreased to 38.

2. **According to the authors “The mean age of the studied population was 9.26±1.92 years old among which 46 (50%) ones were males”. Does 46 patients correspond to 50% of the participants?**
   Dear reviewer, thank you for your notification. You are completely right and 46 boys account for 60.52% of the cases corrected in the revised manuscript. Line 17-18.
3. **The result section is very brief and needs to provide more explanations and details.**
   Dear reviewer. In the revised manuscript it has been tried to expand the presented data of the results section. Lines 177-184.

Reviewer 2:

Dear authors:

Thanks for your submission to the IJPBS Journal. An important subject has been studied in this article. Some points should be revised in this manuscript. Abstract: (page 2)

1. **Where was the study done? Were them inpatient or outpatient?**
   Dear reviewer. Thank you for your comment. The study has been conducted in an outpatient setting. Line 10.
2. **Mention the age range of participants.**
   Dear reviewer, thank you for you comment. It has been added. Lines 17-18.
3. **Were all of them received similar dose of drugs?).**
   Dear reviewer, thank you for your comment. The patients received variable doses of the drugs considering their tolerance and the physician satisfaction of response to the treatment. The detailed information is presented in the method section.

Methods:

Study population (page 5):

1. **Accurate mention your mean about any chronic disorder in patients? (page 5)**

Dear reviewer. Thank you for your comment. The chronic disorders have been added. Line 74-77.

2. **Mention how you assessed drug-related adverse effects? (page 5)**

   Dear reviewer. Thank you for your notification. The mothers were asked about any new onset symptoms or complaints initiated by the interventions. If the symptoms were compatible with the side effects of each drug, and led to significant impairment in the daily activities of the child, the drug use was halted.

3. **Accurate mention how sample size was determined?(page 5)**

   Dear reviewer. Thank you for your comment. Actually, the primary measured sample population for each group accounted for 50 cases, but by the emergence of COVID-19 in 2019, closing of the school and reluctance of the ADHD patients to refer for treatment, we could not gather the required cases and due to the limitations of specialty course in Iran for graduation, the type 1 fault was changed in order to decrease the study population to the gathered one (38 ones in each group).

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   D: Minimum mean difference of Conners score between two groups= 14
   The calculation with these numbers accounted for 46 patients in each group that by considering 10% withdrawal, the number of 50 patients was considered. Nevertheless, due to the problems after COVID-19 outbreak, the 10% withdrawal was increased to 25% and the measurements decreased to 38.

4. **Accurate mention the method used to generate the random allocation sequence?(page5)**

   Dear reviewer. Thank you for your comment. The detailed method of randomization is presented in lines 81-88.

5. **Mention who generated the allocation sequence? (page5)**

Dear reviewer. Thank you for your comment. The random sequencing was provided with the statistical analyst who was blinded to the groups' name; because the patients were allocated to groups 1 and 2, but the medications applied by each group were concealed from the biostatistician.

6. **Mention who enrolled participants and who assigned participants to intervention? (page 5).**

   Dear reviewer. Thank you for your comment. The psychiatrist mentor enrolled the participants and assigned them to the interventions; however, all the assessments done in the course of the study was performed by a resident of psychiatry who was blinded to the applied intervnetions.

7. **Accurate mention about the way of blinding? (page 5)it should describe completely.**

   Dear reviewer. The blinding method has been completely described in the revised manuscript. Lines 89-94

Interventions (page 6):

1- **were all of them received similar dose of drugs? (page 6)**

   Dear reviewer. Thank you for your comment. The recievd dosages among the participants differed considering their response to the treatment and the psychiatrist satisfaction of the received medications.

2- **Mention the maximum dose of methylphenidate in this study? (page 6)**

   Dear reviewer. Thank you for your comment. The maximum dose of MPH accounted for 60 mg per day. Detailed information is presented in the mani manuscript. Lines 98-100.

3- **Did you consider the weight of patients in treating them? (page 6)**

   Dear reviewer. Thank you for your comment. The patients' weight was considered for atomoxetine only, but the others were prescribed in fixed doses and upgraded gradually as mentioned in the manuscript.

4- **How you assessed side effects of drugs? (page 6-7)**

   Dear reviewer. Thank you for your notification. The mothers were asked about any new onset symptoms or complaints initiated by the

interventions. If the symptoms were compatible with the side effects of each drug, and led to significant impairment in the daily activities of the child, the drug use was halted. All the assessments were done via the psychiatrist responsible for the treatment of the patients.

5- **Accurate mention about when you assessed them? In which week or month of study? Page 6.**

Dear reviewer. Thank you for your point of view. It has been described in the revised manuscript. Lines 110-111.

Results:

1- **In the table 2 you mentioned, within a month and within 4 months, but it should mention clearly about were they assessed at same time ? exactly in which week or month? (Page 10).**

Dear reviewer. Thank you for your notification. As it has been mentioned in the method part. The patients received the medications for four months. They were visited at baseline and the within a month and four months after the intervention initiation and the questionnaires were filled in the mentioned visits.

2- **Did you compare them at same dose and at same time?(page 10)**

Dear reviewer. Thank you for your precise notification. The patients were compared at baseline, within a month and four months after the interventions initiation. Therefore, considering the time span, they were assessed in similar pattern, but the dosage might be different in the patients based on their weight in atomoxetine or the physician's request to upgrade or degrade the dosage. However, the applied dosages did not differ significantly.

3- **Did you consider the effect of weight in treating them and in adjusting dose?(page 10)**

Dear reviewer. Thank you for your notification. The doses were adjusted according to weight for ATX only, but treatment with FLX and MPH was done in fixed doses and according to the psychiatrist's discretions.

Nevertheless, all he medications were prescribed considering the international guidelines and similar to the previous studies in the literature.

Discussion: (page 11-13)

1- **mention sources of bias for example: (page 13)**

You didn't adjust the dose of drugs to campare them exactly in this study.

You didn't adjust dose of methylphenidate with the weight of patients.

You didn't compare them exactly at the same time , because time and treatment duration has important effect in response to drugs.

Dear reviewer. Thank you for your comment. The design of the study is similar to other ones in the literature. However, we assume a misconception has occurred for the reviewer about the time of assessment. All the assessments were done at baseline and then, within a month and four months after the interventions. Accordingly, the patients were not assessed in the similar time. Every patient's assessment was done at baseline and in follow-ups if they have taken the medications for a month and four months.

Regarding the dose adjustment, ATX was prescribed based on the weight, therefore the reviewer's expectation has been met. The other two drugs were given considering the response to the treatment and based on the clinical judgement of the mentor.

In general, we assume these two points were not a source limitation.

2- **mention the benefits and harms of each drug regimen(page 13).**

Dear reviewer. Thank you for your precise notification. This part has been added to discussion. Lines 199-205, 209-212 and 241-252

Reviewer 3:

this study needs minor revision.

While thanking the efforts of the respected authors who have addressed an important topic, the problems of the article are presented as follows:

1. **The Ethic code that is noted for this study is different a bit with the title that is mentioned in Iran National Committee for Ethics in Biomedical Research (Efficacy of atomoxetin/ritalin-fluoxetin on anxiety symtoms, ADHD symtoms and function of children).**

   Dear reviewer. We have searched the national site of the ethics in biomedicine (https://ethics.research.ac.ir/) and the code was compatible with what written in the manuscript.

2. **The IRCT code is not available as much as I surfed on the net!**

   Dear editor. Thank you for your precise notification. The corrected IRCT code has been added to the revised manuscript "IRCT20211004052670N2". Line 68.

3. **Please precisely explain how you evaluate the patients for ADHD and Anxiety Disorder?(by KSADS? Unstructured interview?).**

   Dear reviewer. The concurrent ADHD and anxiety disorder was diagnosed through an unstructured interview.

4. **Who Refers the patients?**

   Dear editor. Actually, the patients referred to one of the children subspecialty psychiatry mentors of our center affiliated with our university. She explained the study and medications for their legal guardians. Then, they referred to the psychiatry assistant who was responsible for the study conduction and was blinded to the applied medication. She performed the follow-up visits and completed the questionnaires.

5. **Which type of Anxiety disorder do you mean?(Separation anxiety disorder? social anxiety disorder? GAD? Panic disorder? Specific phobia???)**

   Dear reviewer. We have entered all types of anxiety in the study. In fact an unstructured interview was done and those who were compatible for any of the disorders were included.

6. **What is the reason of age between 6-12 years old?**

   Dear editor. The age range has been mostly selected because of age-limitation for FLX and ATX use and also, the reliability of appropriate drug

taking by the patients. Besides, some of the ADHD patients significantly improve after their 12 years old. Therefore, we selected 6-12 year-old ADHD subjects for this study..

7. **You mentioned that presence of Mood disorder in first-degree family was unmet criteria. How you consider this (self-report? Interview with first-degree family?) in attention to the genetic role in ADHD, possibility of ADHD and its comorbid disorders is high, though this issue didn't make a trouble for you in this study?**

   Dear editor. Thank you for your precise comment. Actually, as the presence of any mood disorder in a family member might affect the other members, we decided to put this criterion as one of the unmet criteria and assess it in the primary interview done by the psychiatrist who was responsible for the baseline assessment of the patients. However, all the patients had medical records in which the familial parameters were entered.

8. **You mentioned that after initiation of methylphenidate(5mg/BD), you increased the dosage, 10 mg weekly, if it is needed. Please note that what was the upper limit of dosage and what was the most receive dose?**

   Dear reviewer. Thank you for your point. MPH was initiated with 5 mg/BD for all patients and increased gradually to achieve the desired response or adverse effects initiation. The maximum dose limitation was 60 mg per day. It is added to the manuscript lines 98-100.

9. **Please precisely explain about sampling method. Based on which formula?**

   Dear reviewer. Thank you for your comment. Actually, the primary measured sample population for each group accounted for 50 cases, but by the emergence of COVID-19 in 2019, closing of the school and reluctance of the ADHD patients to refer for treatment, we could not gather the required cases and due to the limitations of specialty course in Iran for graduation, the type 1 fault was changed in order to decrease the study population to the gathered one (38 ones in each group).

The formula is as following:

$$N=\frac{¿2S^2(Z1+Z2)^2}{D^2}$$

Z1: 95% confidence interval= 1.96,
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D: Minimum mean difference of Conners score between two groups= 14
The calculation with these numbers accounted for 46 patients in each group that by considering 10% withdrawal, the number of 50 patients was considered. Nevertheless, due to the problems after COVID-19 outbreak, the 10% withdrawal was increased to 25% and the measurements decreased to 38.

10. **One group received 2 drug and one took just one, how you explain this difference for participants? Could be it make some influences in double-blindness?**

    Dear editor. Thank you for your comment. However, the person who prescribed the medications and the one who assessed the patients were not similar, it potentially might be a source of a bias and one of the weak points of our study. Nevertheless, the parents were aware of the medications and it was the reason of not using placebo. Besides, the interviewer who was blind to the applied medications knew the patients as group a and b. This point has been added to the limitation section. Lines 262-264.

11. **In table 1, on ATM part, you wrote n=38, but the summation of female and male participants is 40!!!! Please correct this.**

    Dear editor. Sorry for such a great fault. It has been corrected in Table 1.

12. **It’s better to verify that how each treatment regimen effect on 5 domains of conner's test.**

    Dear reviewer. Thank you for your comment. In fact the main scope of our study was to evaluate anxiety status in the patients, not ADHD. Therefore, Conner was assessed as a secondary aim in which ADHD in general was investigated. Accordingly, each of the subscales of Conner in which various ADHD characteristics were evaluated was not significant in this study and we have gathered data of Conner in total.

13. **More than 50% of references is related to more than 5 years ago, so an update is needed.**

    Dear editor. Thank you for your comment. The references have been altered to more novel ones as you requested. References number 7-10 and 30.

    With regards

2 Revision 1

4 comments · 24 Apr 2023 – 29 Apr 2023

Referee 2 Reviewer — MINOR REVISION — 24 Apr 2023

In my opinion, it needs minor revision.

Referee 1 Reviewer — ACCEPT — 25 Apr 2023

Dear authors,
Thank you very much for the revisions.
Best regards

Associate Editor — MINOR REVISION — 25 Apr 2023

minor revision

Editor-in-Chief — MINOR REVISION — 29 Apr 2023

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.

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.

Minor revision:

1. **The Ethic code that is noted for this study is different a bit with the title that is mentioned in Iran National Committee for Ethics in Biomedical Research (Efficacy of atomoxetin/ritalin-fluoxetine on anxiety symptoms, ADHD symptoms and function of children). The title of this article is "Atomoxetine versus the combination of methylphenidate plus fluoxetine for the management of anxiety disorder in ADHD children; a randomized clinical trial". The last two items of first one (ADHD symptoms and function of children).) was not been mentioned in aims of study.**

   Dear reviewer. The mentioned categories are added to the aim of the study in abstract (lines 8-9) and introduction (lines 58-59).

2. **Word counts is more than 3500**

   Dear reviewer.

3 Revision 2

2 comments · 8 May 2023 – 9 May 2023

Associate Editor

ACCEPT 8 May 2023

It's been accepted.

Editor-in-Chief

ACCEPT 9 May 2023

We have completed our review of your manuscript and are pleased to inform you that it is 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.