Re: Concerns regarding your publication in Neurotherapeutics

mahmoud samy <Mahmoud.samy@fop.usc.edu.eg>

Fri 6/17/2022 10:02 PM

To: Gregory Baer <gregory.baer@springer.com>

Cc: esraa.mosalam@phrm.menofia.edu.eg <esraa.mosalam@phrm.menofia.edu.eg>;dr_samy777@yahoo.com <dr_samy777@yahoo.com>;khaledelattar87@gmail.com <khaledelattar87@gmail.com>;dr.samy777@gmail.com <dr.samy777@gmail.com>;yamenma7moud2017@gmail.com <yamenma7moud2017@gmail.com>;esraa_171@yahoo.com <esraa_171@yahoo.com>

Dear Dr. Gregory Baer,

All the authors disagree to the retraction decision. The decision is based on speculations without any evidence that we have violated the ethical oversight. The decision does not follow the Committee on Publication Ethics (COPE) Retraction Guidelines. Neurotherapeutics journal is a member of the COPE and should undergoes its principles. According to COPE's formal policy, retraction should be undertaken when there is a clear evidence that the research findings are unreliable, either as a result of major error (e.g., miscalculation or experimental error), or as a result of fabrication or falsification. The decision to retract our paper was built on an assumption of manipulation. Considering providing the full original data set timely in excel spreadsheet as a clear objective evidence of manipulation is unjustified and unacceptable, particularly when considering that our research was unfunded and was done in research settings in a low middle income country.

According to COPE formal policy, retractions are not appropriate either where the findings are inconclusive or where additional information would sufficiently address these concerns. We do respect and appreciate the editor’s need to establish the integrity of findings. We are willing to submit all the documents needed to support the reported outcomes.

The authors have followed the Neurotherapeutics’ journal instructions under the title “protection of human subjects research” the procedures followed were in accordance with the ethical standards of the institutional ethical committee and with the Helsinki Declaration. It is permissible for phase I/II clinical trials to rely on the monitoring and the oversight of institutional ethics committee. The authors can provide signed formal supporting documents from the head of research ethics committee about the oversight activities undertaken by the institutional IRB in our study.

Once again, our study is a proof-of-concept phase I/II trial and the FDA, and the National Institutes of Health (NIH) and National Institute on Deafness and Other Communication Disorders (NIDCD) stated that all Phase III clinical trials require monitoring by a DSMB. For earlier trials (such as Phase I and Phase II), a DSMB may be appropriate for long term studies that employ particularly high-risk interventions or involve vulnerable populations. Our trial utilized a commonly used safe drug for short term as adjuvant therapy rather than a primary therapy and did not use particularly high-risk interventions or include vulnerable populations. That’s why independent DSMB was not part of the study and was not required by Research Ethical Committee. Furthermore, this role was done by the Research Ethical Committee as stated in the previously attached IRB approval

In addition, we followed the CONSORT guidelines in reporting of our trial findings. The Auditable dataset was not required to get ethical approval nor for the scientific publications. It was also not required by the Research Ethical Committee during monitoring or by the journal's author instructions during submission. Although we are recognizing its importance in evaluating the quality of RCTs, there is no method to keep auditable data set because the output is generated from ELISA software as an Excel sheet. However, we believe that dataset might be a requirement by the FDA or EMA for large clinical trials investigating new agents that were funded by institutions, organizations, or companies.

Based on the forementioned statements the authors disagree to the retraction decision and keep all their rights to take all necessary legal actions towards your decision to protect our reputation. Finally, the retraction decision is unfair to us, and we hope you will reconsider the decision. We have sent our data as requested and clarified the issues with the ethical oversight, the reporting and the availability of audited data for this trial in our previous response.

Sincerely yours,

Mahmoud S. Abdallah

From: Gregory Baer <gregory.baer@springer.com>
Sent: Monday, June 13, 2022 5:35 PM
To: mahmoud samy <Mahmoud.samy@fop.usc.edu.eg>
Cc: esraa.mosalam@phrm.menofia.edu.eg <esraa.mosalam@phrm.menofia.edu.eg>; dr_samy777@yahoo.com <dr_samy777@yahoo.com>; khaledelattar87@gmail.com <khaledelattar87@gmail.com>; dr.samy777@gmail.com <dr.samy777@gmail.com>; yamenma7moud2017@gmail.com <yamenma7moud2017@gmail.com>; esraa_171@yahoo.com <esraa_171@yahoo.com>
Subject: RE: Concerns regarding your publication in Neurotherapeutics

Dear Dr. Mahmoud S. Abdallah and coauthors,

I hope this finds you well. Apologies for the gap in communication.

After assessing your responses, the Editor-in-Chief has decided that the article should be retracted. Please see the retraction wording below:

The Editor-in-Chief has retracted this article. Concerns have been raised about the data presented. The response from the authors to these concerns has shown that there are serious issues with the ethical oversight, the reporting and the availability of audited data for this clinical trial. The Editor-in-Chief therefore no longer has confidence in the results and conclusions presented. [The authors agree/do not agree with this retraction].

I ask that each author please respond individually, stating whether they agree or disagree with the retraction. The final sentence of the retraction notice will be modified to reflect your responses.

Please respond by June 20th.

Thank you,
Greg

From: mahmoud samy <Mahmoud.samy@fop.usc.edu.eg>
Sent: Sunday, March 20, 2022 10:19 AM
To: Gregory Baer <gregory.baer@springer.com>
Subject: Re: Concerns regarding your publication in Neurotherapeutics

[External - Use Caution]

Dear Prof. Gregory Baer,

We have addressed these additional concerns in depth in the sections below.

Comment 1: Sample size and protocol similarity. You state in Response #1 that you estimated a final sample size of 30 per group. However, you enrolled 40 subjects per group. It seems unlikely that an IRB that would permit 33% extra enrollment in an RCT without clear justification. What was your scientific justification and can you provide the IRB documentation that approved a larger sample size than your calculations indicated was necessary?

Response: We stated that our sample size of 40 per group should be sufficient to test our hypothesis. This additional 33% extra enrollment was used to increase the power of the study, which was previously calculated assuming an 80% study power. In addition, it was reported that the dropout rate in controlled trials of antidepressants could reach 25% for many reasons including lack of efficacy or adverse effects (see the reference below). Initially, our calculations assumed 15% dropouts. However, we were concerned if we had higher dropouts this would have an impact on the study's validity. Furthermore, the trial utilized a commonly used safe drug as adjuvant therapy rather than a primary therapy and did not use particularly high-risk interventions or include vulnerable populations. Accordingly, an increase in the number of participants did not expose patients to unnecessary risk. Further, the IRB approval is attached which included approval for the sample size.

Schalkwijk S, Undurraga J, Tondo L, Baldessarini RJ. Declining efficacy in controlled trials of antidepressants: effects of placebo dropout. Int J Neuropsychopharmacol. 2014 Aug;17(8):1343-52. doi: 10.1017/S1461145714000224 . Epub 2014 Mar 13. PMID: 24621827 .

Li F, Nasir M, Olten B, Bloch MH. Meta-analysis of placebo group dropout in adult antidepressant trials. Prog Neuropsychopharmacol Biol Psychiatry. 2020 Mar 2;98:109777. doi: 10.1016/j.pnpbp.2019.109777 . Epub 2019 Nov 5. PMID: 31697973 .

Comment 2: RCT ethics. A randomized, double-blind, placebo-controlled trial generally requires an independent data and safety monitoring board and the data would need to be verified by an independent monitor. Good clinical practice also requires an auditable trail for all clinical and research data generated as part of a trial. No evidence of an independent DSMB was found, and an excel spreadsheet is not

acceptable as a data source for a clinical trial. Please demonstrate that you have auditable data sources. We ask that you provide the IRB approval and address why an independent DSMB was not part of the study. In addition, since the concern is overlap of data in comparison to another publication, we ask that you provide the auditable dataset from the other study as well.

Response: The independent DSMB was not required by Research Ethical Committee as it included a monitoring board, which has monitored the study on a regular basis and approved the pre-publication results. In addition, National Institutes of Health (NIH) and National Institute on Deafness and Other Communication Disorders (NIDCD) stated that all Phase III clinical trials require monitoring by a DSMB. For earlier trials (such as Phase I and Phase II), a DSMB may be appropriate for long term studies that employ particularly high-risk interventions or involve vulnerable populations. Our trial utilized a commonly used safe drug for short term as adjuvant therapy rather than a primary therapy and did not use particularly high-risk interventions or include vulnerable populations. That's why independent DSMB was not part of the study and was not required by Research Ethical Committee.

Regarding the auditable dataset, we recognize its importance in evaluating the quality of RCTs. However, we believe that dataset might be a requirement by the FDA or EMA for large clinical trials investigating new agents that were funded by institutions, organizations, or companies. Auditable dataset was not required to get ethical approval nor was it required for scientific publications. It was also not required by the Research Ethical Committee during monitoring or by the journal's author instructions during submission. In addition, there is no method to keep auditable data set because the output is generated from ELISA software as an Excel sheet. In addition, there was no funding to have a commercial data management system.

Once again, there is no data overlap between the two publications as was established in our previous responses. Metformin and cilostazol are two separate medications from two different therapeutic classes, each with its own mechanism of action. The Research Ethical Committee approved both studies separately, which used two different populations recruited at different times. From scientific overview, the two populations in both trials had major depressive disorders with no other comorbidities. As a result, parallels in study protocols between the two studies are feasible. The mentioned article was published in September 2021 and the article published in neurotherapeutics was in June 2020. The available data and IRB approval for the article published in neurotherapeutics are attached.

Comment 3: Biomarker measurements. All of the analytes were performed using ELISA and you state that the kits were obtained from MyBioSource. There is some controversy over whether MyBioSource ELISAs provide reliable data. Please provide the raw ELISA data output from the spectrophotometer. What were the CVs for the assays? Can you explain why you didn't use a clinical laboratory to measure CRP or vitamin B12? Did you evaluate the performance of each ELISA kit prior to use?

Response: The source for all kits has been specified in the manuscript prior to publication and we do not have any comments during the revision process regarding this point. We cannot find any reliable sources

that reported any controversy over MyBioSource ELISAs. The reviewer did not provide any source nor did the journal warn the scientific community of such allegations. The raw ELISA data output from the spectrophotometer was attached. The CVs were < 10%, < 8%, < 8%, < 8%, < 10%, < 8%, < 8%, < 10%, and < 8% for TNF-alpha, IL-6, IL-1Beta, BDNF, Serotonin, IGF-1, MDA, CRP, and Vitamin B12, respectively.

In terms of CRP and vitamin B12 quantification, we did not use a clinical laboratory because it was not proposed in the approved protocol, and it was cost prohibitive.

Regarding the performance of each ELISA kit, it was tested using spike control method that involved diluting known concentration of standard in serum samples, by background absorbance subtraction, and by performing standard curve for each plate.

Comment 4: Clinical trials.gov NCT0408848 record. There are anomalies in the start and end dates of the study. The original study start date was January 1, 2019 (the first version of the NCT record was posted on Sept 11, 2019). The start date was then modified on April 6, 2020 to retroactively be listed as January 1, 2017. Several prior version edits in between these two dates did not record a 2017 start date. Similarly the primary completion dates have anomalies. On the same April 6, 2020 version, the primary completion date was marked at March 30, 2020 (i.e., primary completion date had passed). This date was then modified 4 days later to report a completion date of July 30, 2020.

Response: First, making corrections on the record as permitted by the guidelines are not “anomalies.” They are corrections. To clarify the record, the study was approved by two institutions as attached, one on January 1, 2017, and the other on January 1, 2018. However, it was registered retrospectively on Clinical trials.gov on Sept 11, 2019. The initial study protocol was approved on January 1, 2017, but it inadvertently listed January 1, 2019, which is why the date was corrected to January 1, 2017. The primary completion date was changed from March 30, 2020, to July 30, 2020, as the patients was followed for longer than the 12-week period based on the recommendation of the Research Ethical Committee to assess if there were any changes for using metformin for longer durations for some of them or any relapse after stopping metformin for the others. Furthermore, all of these adjustments were made prior to publication.

Sincerely,

Mahmoud S. Abdallah; PhD.
Lecturer of Clinical Pharmacy
Faculty of Pharmacy
University of Sadat City, Egypt.
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E-mail: dr_samy777@yahoo.com
Mahmoud.samy@fop.usc.edu.eg

From: Gregory Baer <gregory.baer@springer.com>
Sent: Friday, March 11, 2022 5:34 PM
To: mahmoud samy <Mahmoud.samy@fop.usc.edu.eg>
Subject: RE: Concerns regarding your publication in Neurotherapeutics

Dear Abdallah,

Thank you for your prompt response.

Please address the additional concerns as follows:

Sample size and protocol similarity. You state in Response #1 that you estimated a final sample size of 30 per group. However, you enrolled 40 subjects per group. It seems unlikely that an IRB that would permit 33% extra enrollment in an RCT without clear justification. What was your scientific justification and can you provide the IRB documentation that approved a larger sample size than your calculations indicated was necessary?

RCT ethics. A randomized, double-blind, placebo-controlled trial generally requires an independent data and safety monitoring board and the data would need to be verified by an independent monitor. Good clinical practice also requires an auditable trail for all clinical and research data generated as part of a trial. No evidence of an independent DSMB was found, and an excel spreadsheet is not acceptable as a data source for a clinical trial. Please demonstrate that you have auditable data sources. We ask that you provide the IRB approval and address why an independent DSMB was not part of the study. In addition, since the concern is overlap of data in comparison to another publication, we ask that you provide the auditable dataset from the other study as well.

Biomarker measurements. All of the analytes were performed using ELISA and you state that the kits were obtained from MyBioSource. There is some controversy over whether MyBioSource ELISAs provide reliable data. Please provide the raw ELISA data output from the spectrophotometer. What were the CVs for the assays? Can you explain why you didn't use a clinical laboratory to measure CRP or vitamin B12? Did you evaluate the performance of each ELISA kit prior to use?

Clinical trials.gov NCT0408848 record. There are anomalies in the start and end dates of the study. The original study start date was January 1, 2019 (the first version of the NCT record was posted on Sept 11, 2019). The start date was then modified on April 6, 2020 to retroactively be listed as January 1, 2017. Several prior version edits in between these two dates did not record a 2017 start date. Similarly the primary completion dates have anomalies. On the same April 6, 2020 version, the primary completion date was marked at March 30, 2020 (i.e., primary completion date had passed). This date was then modified 4 days later to report a completion date of July 30, 2020.

I look forward to receiving your responses.

Thank you,
Greg

From: mahmoud samy <Mahmoud.samy@fop.usc.edu.eg>
Sent: Sunday, March 6, 2022 2:12 PM
To: Gregory Baer <gregory.baer@springer.com>
Subject: Re: Concerns regarding your publication in Neurotherapeutics

[External - Use Caution]

Dear Gregory Baer,

We are extremely grateful for allowing us to reply to these concerns. Even though the three published articles have used different agents, these concerns seem to be focused on numbers or indicators regardless

of the scientific aims of the articles. The comments seem to suggest commonalities among article when none exists. However, we have addressed these concerns in depth in the sections below.

Comment 1: This article uses identical protocols and sample sizes to another, previously published article: https://www.karger.com/Article/Abstract/492619.

Response: It seems that the reviewer is wondering why scientific protocols that were approved by the ethical committees could be similar. It is because they are well-accepted scientific protocols and were approved by the institutional review board. The previously published article https://www.karger.com/Article/Abstract/492619 has tested the anti-inflammatory and neurotrophic activity of the phosphodiesterase inhibitor pentoxifylline, which belongs to a therapeutic class that is totally different from metformin. In the article published in neurotherapeutics, we have repurposed the antidiabetic metformin that belongs to different therapeutic class and works by different mechanism as adjuvant therapy based on its anti-inflammatory, antioxidant, and neurotrophic activity using the protocols in our previously published work which is also similar to many other published studies (See list below). These studies used other agents as adjuvant or adjunct in the treatment of major depressive disorders including celecoxib, simvastatin, and pioglitazone. Moreover, the protocols used in all trials were commonly used and approved by our health institutions in diagnosis and rating of patients with major depressive disorders.

Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress Anxiety. 2009;26(7):607-11.

Sepanjnia K, Modabbernia A, Ashrafi M, Modabbernia MJ, Akhondzadeh S. Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: randomized double-blind placebo-controlled trial. Neuropsychopharmacology. 2012 Aug;37(9):2093-100. doi: 10.1038/npp.2012.58 . Epub 2012 May 2. PMID: 22549115 ; PMCID: PMC3398722 .

Gougol A, Zareh-Mohammadi N, Raheb S, Farokhnia M, Salimi S, Iranpour N, et al. Simvastatin as an adjuvant therapy to fluoxetine in patients with moderate to severe major depression: A double-blind placebo-controlled trial. J Psychopharmacol. 2015;29(5):575-81.

Regarding the sample size, it was calculated and mentioned on the manuscript based on a previous meta-analysis of antidepressant treatment trials showed that placebo treatment has an average effect size of a 1.69 compared to 2.50 for an antidepressant treatment (See reference below). Using an 80% power and two-sided significance of 5% with an effect size of 0.81, sample size was 26 subjects per group. A final sample size of 30 subjects was estimated, assuming a 15% attrition rate. Therefore, our sample size; 40 per group, should have enough power to test our hypothesis.

Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG. Meta-analysis of the placebo response in antidepressant trials. J Affect Disord. 2009;118(1):1-8.

Comment 2: In Table 1 of the metformin study, mean age was 35.1 in the placebo group and 34.05 in the metformin group; mean ages were exactly 3 years greater for both groups in the cilostazol trial (38.1 and 37.05).

Response: The study included different populations that were recruited at different times. It is possible that some of the age group would be similar. It is not clear what issue this comment is trying to raise. There are no common numbers shared between the articles. The reviewer seems to point at the difference in values while ignoring that both the mean and the standard deviation are different. Regardless, the raw data are attached to this response to clarify how they the mean and average were calculated. In addition, the mentioned article was published in September 2021 and the article published in neurotherapeutics was in June 2020.

Comment 3: A whole host of specialized biomarkers were tracked during the study. There is overlap in these values between this paper and one in CNS Neuroscience & Therapeutics (https://onlinelibrary.wiley.com/doi/10.1111/cns.13731) , e.g. placebo TNF-alpha 10.22 (1.42) --> 11.12 (3.42); study drug TNF-alpha 10.58 (1.28) --> 11.58 (3.58).

Response: Firstly, the mentioned article was published in September 2021 and the article published in neurotherapeutics was in June 2020. Secondly, there is no overlap in these values as alleged in the comment. Once again, the mean and the standard deviation are totally different in both placebo and study drug before and after treatment in the two articles. From scientific overview, the two populations in both trials were major depressive disorder with no other comorbidities. Accordingly, it is possible that the levels of the inflammatory cytokines would be non-significantly different between the two studies.

Comment 4: Patients were assessed and excluded for the trials only in multiples of ten (e.g. 120 assessed, 20 excluded due to medical illness, 10 declined, 10 with misuse of drugs; 140 assessed, 20 excluded due to medical illness, 40 declined to participate). In this paper and the paper in CNS Neuroscience and Therapeutics mentioned above, your randomization happened to assign the same number of patients (40) to each arm, identical numbers of patients discontinued active drug and placebo (3 in one paper, 4 in the next), and no patients were ever lost to follow-up.

Response: Like the previous comments, this comment is trying to make a correlation between two studies. As we mentioned above the article in CNS Neuroscience and Therapeutics was published in September 2021 and the article in neurotherapeutics was published in June 2020. Moreover, the number of the excluded patients due to the misuse of the drug does not follow the alleged ”multiples of ten” as claimed, and the number that declined to participate was totally different. Regarding the dropouts, we expected high dropouts in both trials, but we were surprised that only three patients in one paper and four patients in the other in both groups have dropped. The low dropout rate may be attributed to the short period of the trial (6 weeks or 12 weeks). In addition, the study was carried out in the University Hospital in which all patients including the patients in our trial received a free medical insurance service that encouraged them to strictly adhere to the medication. Moreover, the patients were followed up weekly by

phone for assessment of compliance to the study medication, adverse events, and for any other issues. Thus, dropouts from the therapy due to insufficient efficacy or adverse events appeared to be limited. Furthermore, the demonstrated efficacy could be detected in the early therapeutic phase by the patients. It was speculated that early signs of improvement most likely led to increased adherence, which in turn, led to prevention of relapse and recurrence and represented major benefit to patients that desire to be reintegrated into society.

Comment 5: Reviewing the clinicaltrials.gov record for the cilostazol trial, it appears that in January 2021 (when the trial had ostensibly already been recruiting for 18 months and was only 3 months from completion) the treatment duration was changed from 12 weeks to 8 weeks (https://clinicaltrials.gov/ct2/history/NCT04069819?A=1&B=6&C=merged#StudyPageTop).
Three weeks later, it was changed again from 8 weeks to 6 weeks (https://clinicaltrials.gov/ct2/history/NCT04069819?A=6&B=7&C=merged#StudyPageTop).

Response: First, this comment is not relevant to the study in Neurotherapeutics. The clinical trials are for a completely different drug. So, it is not clear why the reviewer is referencing this trial. Second, we have addressed these changes according to the guidelines. The initial study protocol was prepared to be 12 weeks; however, the institutional review board decreased the study duration to be 6 weeks. We corrected that but inadvertently listed 8 weeks. After we figured out this unintended mistake, we changed the duration from 8 weeks to be 6 weeks. Again, this is a procedural issue that has nothing to do with the study published in Neurotherapeutics.

Comment 6: The numbers of patients experiencing adverse effects with metformin vs. placebo differed by 1 for almost every single adverse effect (e.g. 5 had nausea with placebo, 6 with metformin).
Response: The reviewer is pointing to the small differences in the adverse effect while ignoring the fact that the numbers themselves are small. Further, Metformin is a well-tolerated drug that is widely used among diabetic patients without major side effects. Moreover, the reported adverse effects were at the end of the trial. The patients may tolerate the minor side effects of the used drugs. This could explain the small number and difference in both groups. Moreover, the side effects regarding increase or decrease appetite differ by 2 between the two groups. We reported the side effects based on the patients complains using checklist.

Comment 7: There were no statistically significant differences in any baseline clinical factors, nor in any of the 9 different baseline biomarkers looked at. In contrast, p values for every single clinical outcome were 0.000, and p values for 8 of 9 biomarker outcomes were 0.000 (the one nonsignificant one was B12 levels decreasing with metformin, but not significantly different compared to placebo).
Response: The none statistically significant differences in any baseline clinical factors may be due to the non-significant differences in the demographics data among the participants, collecting blood samples at the same time (fasting morning sample), and the average of duplicated readings for each measurement was recorded according to the manufacture protocol. (See attached example for TNF-alpha statistics).

Furthermore, we have explained the improvements in these clinical factors after the treatment in the published article as follow:

Our findings were consistence with other studies, which reported that MET decreases the expression of IL-1β and IL-6 regardless of the diabetes status (39, 40). Moreover, MET decreases TNF-α -mediated gene expression of pro-inflammatory and cell adhesion molecules to inhibit endothelial cell inflammation (41, 42). In fact, reduced level of the pro-inflammatory cytokines leads to increased bioavailability of serotonin through regulation of multiple metabolic pathways (43, 44). MET affects brain plasticity through modulation the levels of neurotrophic factor including BDNF by activation of AMP-activated protein kinase (AMPK) and cAMP-response element binding protein (CREB) as reported in preclinical models (45). More specifically, MET increases the expression of BDNF by enhancing CREB phosphorylation and promoting histone acetylation while increasing the synaptic structures' plasticity (45). Moreover, MET has been reported to reduce IGF-1 levels, endogenously developed reactive oxygen species (ROS), and DNA damage (46).

Regarding to the placebo group, fluoxetine has anti-inflammatory effect, which mediated by reducing the pro-inflammatory cytokines as well as the expression of free radicals (51, 52). Moreover, fluoxetine can induce immunomodulatory effect through its impact on serotonergic neurons in the central nervous system (53). These properties of fluoxetine could disclose the significant decrease in the serum levels of TNF–α, IL-1β, IL-6, IGF-1, MDA, CRP alongside with the significant increase in the serum levels of BDNF and serotonin relative to their baseline values. Our results were in line with other studies reported that fluoxetine could reduce IGF-1 serum level (17) and increase the level of BDNF (54) in depressed patients.

Comment 7: The paper suggests that an immense amount of expensive laboratory testing was done on each of enrolled patient, at multiple time-points, without any funding.

Response: First, it is not clear what the reviewer means by "immense amount." The paper uses common laboratory testing that is available for purchase. Further, the University provided free medical insurance services to the study participants. Third, the expenses were self-funded by the seven authors with some authors funding larger part than others. Finally, our universities support some of the expenses by providing publishing awards to the authors.

Sincerely,

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Lecturer of Clinical Pharmacy
Faculty of Pharmacy
University of Sadat City, Egypt.
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From: Gregory Baer <gregory.baer@springer.com>
Sent: Friday, March 4, 2022 11:09 PM
To: mahmoud samy <Mahmoud.samy@fop.usc.edu.eg>
Cc: esraa.mosalam@phrm.menofia.edu.eg <esraa.mosalam@phrm.menofia.edu.eg>; dr_samy777@yahoo.com <dr_samy777@yahoo.com>; khaledelattar87@gmail.com <khaledelattar87@gmail.com>; dr.samy777@gmail.com <dr.samy777@gmail.com>; yamenma7moud2017@gmail.com <yamenma7moud2017@gmail.com>; esraa_171@yahoo.com <esraa_171@yahoo.com>
Subject: Concerns regarding your publication in Neurotherapeutics

Abdallah, M.S., Mosalam, E.M., Zidan, AA.A. et al. The Antidiabetic Metformin as an Adjunct to Antidepressants in Patients with Major Depressive Disorder: A Proof-of-Concept, Randomized, Double-Blind, Placebo-Controlled Trial. Neurotherapeutics 17, 1897–1906 (2020). https://doi.org/10.1007/s13311-020-00878-7

Dear Dr. Abdallah,

I am the Publishing Editor for Neurotherapeutics. I am contacting you regarding your publication in our journal detailed above.

I am writing to inform you that concerns have been raised about the data presented in your publication. The concerns are as follows:

-This article uses identical protocols and sample sizes to another, previously published article: https://www.karger.com/Article/Abstract/492619

-In Table 1 of the metformin study, mean age was 35.1 in the placebo group and 34.05 in the metformin group; mean ages were exactly 3 years greater for both groups in the cilostazol trial (38.1 and 37.05).

-
- -A whole host of specialized biomarkers were tracked during the study. There is overlap in these values between this paper and one in CNS Neuroscience & Therapeutics (https://onlinelibrary.wiley.com/doi/10.1111/cns.13731), e.g. placebo TNF-alpha 10.22 (1.42) --> 1*1*.12 (3.42); study drug TNF-alpha 10.58 (1.28) --> 1*1*.58 (*3.5*8).
  -Patients were assessed and excluded for the trials only in multiples of ten (e.g. 120 assessed, 20 excluded due to medical illness, 10 declined, 10 with misuse of drugs; 140 assessed, 20 excluded due to medical illness, 40 declined to participate). In this paper and the paper in CNS Neuroscience and Therapeutics mentioned above, your randomization happened to assign the same number of patients (40) to each arm, identical numbers of patients discontinued active drug and placebo (3 in one paper, 4 in the next), and no patients were ever lost to follow-up.

-Reviewing the clinicaltrials.gov record for the cilostazol trial, it appears that in January 2021 (when the trial had ostensibly already been recruiting for 18 months and was only 3 months from completion) the treatment duration was changed from 12 weeks to 8 weeks (https://clinicaltrials.gov/ct2/history/NCT04069819?A=1&B=6&C=merged#StudyPageTop). Three weeks later, it was changed again from 8 weeks to 6 weeks (https://clinicaltrials.gov/ct2/history/NCT04069819?A=6&B=7&C=merged#StudyPageTop).

-The numbers of patients experiencing adverse effects with metformin vs. placebo differed by 1 for almost every single adverse effect (e.g. 5 had nausea with placebo, 6 with metformin).

-There were no statistically significant differences in any baseline clinical factors, nor in any of the 9 different baseline biomarkers looked at. In contrast, p values for every single clinical outcome were 0.000, and p values for 8 of 9 biomarker outcomes were 0.000 (the one nonsignificant one was B12 levels decreasing with metformin, but not significantly different compared to placebo).

-The paper suggests that an immense amount of expensive laboratory testing was done on each of enrolled patient, at multiple time-points, without any funding.

Please can you provide a response to these concerns, along with the raw data for the experiments used in your paper published in Neurotherapeutics?

I look forward to hearing from you by March 11, 2022.

Kind regards,
Greg

Gregory Baer
(he/they)
Editor
Journals, Medicine & Life Sciences

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