**Dear editor**

Thank you for the review of our manuscript for publication in *Expert Opinion on Drug Metabolism and Toxicology*. Following reviewer comments, we have extensively revised the manuscript. We are resubmitting the revised version **“Deep Learning Neural Network Derivation and Testing to Distinguish Acute Poisonings”** for your consideration. If you feel the changes have not adequately addressed any issue, we would look forward to further revising it. Please find below a point-by-point listing of changes in response to reviewer comments.

**Best Regards**

Omid Mehrpour, MD

Associate Professor of Medical Toxicology

Data Science Institute, Southern Methodist University, Dallas, Texas, USA.

Email: omehrpour@smu.edu

Dear Dr. Mehrpour,

Thank you for your patience while your manuscript was under review. Your manuscript, entitled "Deep Learning Neural Network Derivation and Testing to Distinguish Acute Poisonings", which you submitted to Expert Opinion On Drug Metabolism and Toxicology, has now been reviewed. The referee comments are included at the bottom of this letter.

The referees would like to see some revisions made to your manuscript before it can be considered any further. Therefore, I invite you to respond to the referees’ comments and editorial comments below and submit a revised manuscript by 18-Jan-2023.

PLEASE NOTE: When you revise your manuscript please highlight the changes you make in the manuscript by using the track changes mode in MS Word or by using bold or coloured text.

Because we are trying to facilitate timely publication of manuscripts submitted to Expert Opinion On Drug Metabolism and Toxicology, your revised manuscript should be uploaded by the due date specified above. If it is not possible for you to submit your revision by this date, please do let me know as soon as possible.

Once again, thank you for submitting your manuscript to Expert Opinion On Drug Metabolism and Toxicology and I look forward to receiving your revision.

Sincerely,

Sharon Salt

Expert Opinion On Drug Metabolism and Toxicology

**Comments from the Editorial Office to the Author** (important - please ensure that a response is provided for each comment listed below in order to avoid delays with processing your revised manuscript submission):

**RE:** We are grateful for the suggestions that helped to improve the quality of the paper. We revised our manuscript based on your useful suggestions and comments, and hopefully, our revision has improved the manuscript.

•    Please complete and upload the attached author disclosure form. In addition, please include a Declaration of Interest section, at the end of the manuscript. This section should include any sources of funding, along with any financial/other relationships for each author (such as consultancies, employment, expert testimony, honoraria, speakers bureaus, retainers, stock options or ownership).

**RE:** The completed form has been uploaded. Also, Declaration of Interest section has been completed.

•    Please could you confirm if the following funding statement is correct, and insert any relevant grant numbers, if applicable:

-    This paper was not funded.

**RE:** Yes, this statement is correct

•    Please could you confirm if the following declaration of interests statement is correct:

-    The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

**RE:** Yes, this statement is correct

•    Section numbering: please ensure each section heading/subheading in the main body of text is numbered (Your introduction should be numbered 1 and any subheadings therein 1.1, 1.2, 1.3 and so on etc). The Abstract does not need to be numbered. Please include appropriate subheadings, and ensure these are numbered sequentially.

**RE:** Agreed and amended

•    References: I would be very grateful if you could check that your references match our house style:

o    References should be numerically listed in the reference section in the order that they occur in the text.

o    Please ensure no references are duplicated in the reference list.

o    References should appear as a number i.e., [1,2] in the text in square brackets. (Please move any superscript reference citations, to inside the sentence-end punctuation). All reference citations in the text should appear at the end of the sentence, prior to punctuation. (e.g., “….[2].”

o    Please follow our required reference format: Author A, Author B, Author C, et al. Title of article. Abbreviated Journal Title. Date; volume(issue):pages. Please list all authors where there are fewer than four.

o    Please include your websites / patents in the main reference list – if citing a website, please ensure your access date is also included. If you have included a weblink in the main text, please change this to a numbered citation and include it within the reference list.

o    Annotations for your references: 4-8 references should be chosen from your bibliography and highlighted as being ‘\*’ – of interest, or “\*\*” – of considerable interest, with a brief sentence explaining why in each case.

o    For an Endnote referencing style, please click the following link: <https://endnote.com/style_download/tf-standard-nlm/>

o    For more information on our referencing style, please look under the heading ‘Journal’ on page 3 in the following link: [https://www.tandf.co.uk//journals/authors/style/reference/tf\_NLM.pdf](https://www.tandf.co.uk/journals/authors/style/reference/tf_NLM.pdf)

**RE:** the reference list has been modified according to journal guideline.

•    Tables 1-3 and Figures 1-4: please ensure that:

i.    Tables and figures are cited in the text

**RE:** All tables and figures have been cited in the text.

ii.    Tables are in an editable format i.e., .doc, .xls, .ppt

**RE:** Tables are in an editable format

iii.    Study references are separated into a separate column in tables. References in tables should be numbered as if they have appeared in the main body of text where the table was first cited.

**RE:**

iv.    Footnotes contain all abbreviations, symbol information and permission blurbs.

**RE:** The abbreviated terms has been explained in the footnotes of tables

v.    Please provide legends for all of your figures and tables, in a separate section at the end of the document.

**RE:** Agreed and amended

vi.    Figures are in the form that they should appear in the final publication. Please note that no editing of figures will occur during the copyediting/typesetting stage, so it is important that they are correct at this stage.

**RE:** Agreed

vii.    Where necessary, permission has been obtained for any re-use/adaptation of figures and tables sent to us. If any of the figures or tables you have included are unoriginal, copyright permission for their use will need to be obtained from the original publishers. Most major publishing companies have instructions on how to obtain permission on their websites, usually with an online request system. If you have any problems with this, please let me know. Please could you confirm: a) whether your figures/tables are original, or b) whether your figures/tables are adapted or reprinted?

**RE:** All data, tables, figures, etc. used in the manuscript are original, and this study complies with current ethical considerations.

•    Please note that in order to maximize exposure to articles published within the journal, we now publish the accepted, non-typeset version of all accepted manuscripts within a few days after acceptance. Therefore, please ensure that the submitted version of your revised manuscript is in the form that you would wish it to appear in this version published online (figures and tables should still be uploaded as separate files), in case it is accepted following submission of your revision. Once a manuscript has been through our production process (including typesetting), the finalized, typeset version of the article will replace the pre-typeset version online.

**RE:** Agreed

ORIGINAL RESEARCH-SPECIFIC COMMENTS:

•    Please check to ensure p-values have been included wherever significance is claimed. Please add leading zero before all p-values (as per journal style). Include as much data as possible. A p-value or confidence interval must always be cited when data are presented, compared, when a claim is made, or the word significant or significantly is used, including in the abstract.

**RE:** We confirm that all corresponding statistic values are provided in the result section

•    Please include the following headings in your abstract: Background, Research design & methods, Results, Conclusion.

**RE:** Revised

•    If your manuscript describes a clinical trial, the trial must be registered in a public repository, with the registry name and trial registration number included in the abstract and the Methods section of the paper. Retroactive registration is acceptable as long as the date of registration is included in the above mentioned sections of the manuscript.

**RE:** It’s not applicable

•    ETHICS APPROVAL & INFORMED CONSENT: If your manuscript describes a clinical trial, please confirm that the research was conducted with approval from a formal ethics review committee (or followed the principles of the Declaration of Helsinki) and with written consent from the patients. This information should be included in the Methods section of the manuscript.

**RE:** It’s not applicable

**Comments from the Referees to the Author:**

**Referee 1**

The manuscript attempted to develop DNN models which may predict the most probable agent a poisoned patient has been exposed to among eight possible drugs based on clinical features. It's an interesting and valuable topic. But it is felt that the study in its current cannot be accepted and still needs major rework.

**RE:** We are grateful for the suggestions that helped to improve the quality of the paper. We revised our manuscript based on your useful suggestions and comments, and hopefully, our revision has improved the manuscript.

1. I cannot find the codes and data. For DNN study, this issue must be resolved before the paper is accepted. Please provide this.

**RE:** Thanks for the comment. We have posted the code in the following publicly accessible git repository at <https://github.com/ashiskb/npds-workspace> . The dataset was retrieved from National Poison Data System (NPDS) <https://www.aapcc.org/national-poison-data-system> in December, 2019 under a data non-disclosure agreement, therefore we are unable to upload the original NPDS data besides the results. We have provided a link to the data site where a request to retrieve the data can be made easily.

2. The application domain of models need to be defined. The poisonings other than these 8 drugs are impossible to predict using the proposed models.

**RE:** Thank you so much for bringing this point. We agree with your comment. This was a pilot study and we included eight common single-agent poisonings. Further research for developing these models considering more drug agents and multiple exposures is needed. This point has been highlighted as a limitation of this study.

3. The definition or composition of a test or validation set needs to be clarified.

**RE:** Thanks for your comment. Data randomly were divided into three separate sets: training, validation, and testing. The validation set is used to determine optimal hyper-parameters for the models that are fit with the training dataset. Finally, the trained model is evaluated on the testing dataset to provide an unbiased estimate of model performance.

|  |
| --- |
| Revised text in the revised manuscript: |

4. As can be seen from Table 1, there is a serious imbalance between different categories of data. I don't think this metric "overall accuracy" is meaningful in such study.

**RE: <@TODO: Ashis**

1: oversampling the minoritized categories, and then re-train, re-evaluate.

2: Weighted classifiers.

3: Besides (per-class) Precision, Recall, F1-measure.

**>**

|  |
| --- |
| Revised text with emphasis on data imbalance… |

**Referee 2**

In the work reporting, acute poisonings of a predetermined list of medications and authors have intended to build a deep learning system that predicts the most likely agent a poisoned patient was exposed to. They have used data from the National Poison Data System (NPDS) and two Deep Neural Networks (PyTorch and Keras) to perform multiclass classification tasks. They have identified that the best performance was achieved in the diagnosis of single-agent poisoning by sulfonylureas, acetaminophen, benzodiazepines, and aspirin.

However, some concerns need to be addressed before considering this manuscript for publication. I have listed these issues below:

**RE:** We sincerely thank the reviewer for thoughtful consideration of our manuscript and highlighting areas that benefited from revision. We hope that the revised manuscript will now be acceptable.

1) The author should add a graphical abstract so that the paper could be more comprehensible to the readers.

**RE: <@TODO: Ashis, Omid**

\* draw.io to sketch a flowchat.

\* @TODO: Omid:: Send Ashis some examples.

**>**

2) The authors must highlight the complexity of polysubstance exposure discussed in the paper.

**RE:** Thank you so much for bringing this point. Complex pharmacological interactions between substances can lead to unwanted effects and different presentations. Poly-substance exposure alters the medication's effect on the body and it may cause unexpected side effects, delay, decrease, or enhance the action of either drug. So, we considered only single-agent exposures that may limit the generalizability. This point has been highlighted in the text.

3) Details of the Keras framework are missing from the methodology section.

**RE: <@TODO: Ashis**

**\* Kera’s model .summary + graphical representation + VGG based network architecture diagram.**

**>**

4) The author could provide a tabular representation of certain examples of clinical overlaps for single-agent poisonings discussed in the methodology section.

**RE: <@TODO: Omid**

**\* Find good examples of patterns…**

5) Conclusion section could be more elaborative.

**RE:** Agreedand amended

In my perspective, the findings of this study are worthy of publishing. However, before publishing, the work requires some modification.

**Referee 3**

The authors explicitly state the 'pilot' (and thus somewhat preliminary) character of the study and this is important and the authors must be complimented for this specification.

**RE:** We sincerely thank the reviewer for thoughtful consideration of our manuscript and highlighting areas that benefited from revision. We hope that the revised manuscript will now be acceptable.

1) My basic concern is that 131 features are very difficult to ascertain in 'real world' conditions of patients coming to the an emergency room. That is to say that, in my opinion, the work can greatly benefit by a drastic reduction of scored symptoms in order to find a reduced set of 'most relevant descriptors' that in turn can be fed into the ML process to see if the system keeps (or at least does not degrade too much) its performance.

This selection can be made in many ways but I suggest the Legendre algorithm (INDVAL, see: <https://www.sciencedirect.com/science/article/pii/S1476927119302440>).

Thus I push the author to check this possibility that in turn can be profitably used for ameliorating the 'explainability' of the ML procedure (see <https://www.sciencedirect.com/science/article/pii/S2666389920300258>).

**RE: <@TODO: Ashis**

**\* INDVAL / ranking features**

**\* RAIWidget / SHAP / LIME**

[**>**](https://apis.mail.yahoo.com/ws/v3/mailboxes/@.id==VjN-G0RXVD6QJaV21EGlTjOTPSfpggsdVxjGPwzQCBRV8q1Ir1i4WDvJrX7kIpHcwf5KUWhjIv2uHVC2R0Wv8Q9VgQ/messages/@.id==AG8aTF4KQa35Y7cLDQs-6OISq6k/content/parts/@.id==2/refresh?appid=YMailNorrinLaunch&ymreqid=0d3207ab-7bff-450e-1cda-f50000013c00)