

## Scientific Editing Report

### *BUPRENORPHINE FOR THE TREATMENT OF AUTONOMIC DYSFUNCTION SECONDARY TO OPIOID WITHDRAWAL*

#### **SUMMARY**

This manuscript reports that opioid-dependent individuals have elevated levels of catecholamines (particularly norepinephrine and epinephrine) three days after cessation of opioid use, indicative of catecholamine toxicity. Although these elevations were mitigated to a certain degree, the toxicity persisted, resulting in the researchers calling an emergency halt to the study. The manuscript also reports that responses to an Autonomic Dysfunction Scale and Opioid Cravings Scale indicated that buprenorphine was effective in alleviating the symptoms of autonomic dysfunction and in mitigating the participants' cravings for the opioids. Finally, the DNA of the participants was found to be hypermethylated, and existing methylation analysis methods are suitable for studying the DNA of opioid users. The manuscript concludes that additional research on this topic is urgently needed.

The manuscript includes a large amount of information from previous studies, and the general motivation of the study is conveyed in the Abstract. However, the article lacks important information that is needed to help the reader understand the context of the study, the findings obtained and what new information this study contributes to the field. To help with this, we recommend ensuring that the overall objective of the study is clearly presented and that the relationship of all of the analyses to that overall objective is clear. Finally, we think it will be important to ensure that information is placed in the most appropriate section and that an appropriate level of detail is included throughout. We believe that addressing these points will help with conveying the scope and implications of the study to its intended readers.

#### **Guide to the Scientific Edit**

- **Throughout:** Although the overall context of the study is generally well presented, we think that the overarching narrative would be improved by including a more focused explanation of the rationale for the study and a direct statement of the overall study aim in the Abstract and Introduction. Then, we recommend adding transition elements (introductory and concluding sentences) to help lead the reader through the rationale for each of the study components and their relation to the study aim in the Results and to highlight key findings and themes in the Discussion. Together, we believe that this framework will allow the manuscript to emphasize how the findings advance the field.
- **Throughout:** We also think that reorganizing the presentation of the information would help the reader more easily follow the narrative and understand how the different ideas described are related. We have provided suggestions on how to rearrange such that each section of the manuscript can achieve its purpose and lead the reader through the different aspects of the study in our comments in the text and suggest using transitional phrases and sentences to further emphasize the connections between ideas as well as how all of the aspects of the study are related to the stated main aim. Nevertheless, we recommend checking the guidelines of the selected journal to ensure each section contains the necessary information.
- **Throughout:** We also noted some opportunities to use more specific descriptions or phrasing and to ensure that supporting information is appropriately referenced throughout the manuscript.

- **Title:** The Title describes one of the aims of the study well, but we feel that a Title that captures the overall objective might better reflect the importance of the study. We have included a comment with an example you could use to achieve this goal.
- **Abstract:** The first paragraph of the Abstract appears to lay a good foundation that summarizes the key points of the manuscript. However, as written, the entire section is very long, and contains details that are better suited to the main text. Our comments indicate where text can be moved to other parts of the paper and where additional details can be added to the first paragraph to best reflect the most important parts of your study.
- **Abstract:** The Abstract provides much of the information needed to understand the study. However, we think that the specific rationale for the study may be somewhat difficult to identify from the Abstract as written. We have provided suggestions in comments in the manuscript where we think additional detail would be helpful to clarify why the study was performed for the reader. This brief description of the knowledge gap that the study aimed to address should then ideally culminate in a statement of the overall aim of the study, to clearly show the reader how the study addressed the knowledge gap, before the findings are described.
- **Introduction:** The Introduction provides a list of studies that have previously investigated different aspects of the current manuscript. However, it is difficult to understand the overall motivation and objective of the study from this section alone; consequently, we have suggested ways in which you can integrate information from the current Abstract to better flesh out the narrative of the background for your study by presenting the information pertaining to your rationale from the more general to the specific while still referencing the included studies.
- **Introduction:** We also think that it will be important to state the knowledge gap that the study aimed to address at the end of the penultimate paragraph of the Introduction. Ideally, this statement should tie together the ideas presented in the Introduction and directly state the remaining problem or question the work addressed and should logically lead to the overall aim of the study.
- **Introduction:** We recommend beginning the final paragraph of the Introduction by describing the main aim of the study. Then, the paragraph should ideally convey the overall experimental approach used to address this aim, including the study population and various assessments performed, and the main conclusions of the work. We believe that structuring the final paragraph of the Introduction in this manner will help clarify the scope of the study for the reader.
- **Methods:** The Methods section currently offers a summary of what appear to be the key steps in your Methodology. However, it does not appear to provide sufficient detail for all the results to replicated, and in some cases, it also omits information that readers will need to fully understand the results. We believe this section would benefit from the inclusion of some additional information, such as more detailed descriptions of the different participant groups, how they were recruited and the questionnaire development. Some of this information is presented in the Abstract, but we believe that it will be important to provide further information on some of the more important aspects of the methodology to allow your readers to fully understand the study design.
- **Results:** The Results section, as written, summarizes the outcomes of your study but appears to primarily focus on the conclusions drawn from your findings, many of which do not appear to be quantified. In various places in the Results section, we have noted where it would be beneficial to reference the actual data that has been obtained in your study so that the readers can understand how you arrived at the conclusions you have drawn from them.

- **Figures, tables and legends:** A number of the figures and tables present the data from the study and allows them to be visualized easily. We have included comments related to both the figures and tables themselves and their legends on ways to ensure that the data can be clearly read and on ensuring that the legends allow the figures to be interpreted without requiring referral to the text.
- **Discussion:** This section appears to be primarily dedicated to redescribing the findings and providing background information. We think that this section could be used more effectively to present a detailed and in-depth analysis of the findings in the context of the wider field. To help achieve this, after providing a summary paragraph, we suggest devoting the rest of the section to discussing a small number of main themes or topics based on the findings presented in the Results. Each of these themes should be presented in a dedicated paragraph that begins with a clear statement of the theme, goes on to discuss that theme in the light of data from the current study and previously published studies, and ends with a concluding statement that highlights the specific way(s) in which the current study advances our understanding of that theme, and/or points to future directions based on the new information that the current study provides about that theme.
- **Discussion:** To ensure that the full potential impact of the study is clear to readers, we recommend providing additional descriptions of how the findings relate to and/or advance the existing knowledge in the field. We have noted places where we suggest providing such information in the text.
- **Conclusions:** As currently written, it appears that many of the conclusions for the individual experiments and the study as a whole are written in various locations throughout the manuscript. We recommend taking that text and crafting a concluding paragraph that summarizes these extrapolations succinctly in the context of the study aim and provides concrete ideas for how the study findings can be used to further advance the field or to develop additional studies for verification.

### **Possible Journals for Consideration**

Below we discuss the suitability of a range of journals. Please bear in mind that we are editorially independent from Springer Nature journals, and we have not consulted with any journal. Our comments represent only opinion, based on our understanding of the current text.

High levels of catecholamines in the body can result in toxicity, and this toxicity has been previously reported in a number of different contexts. The finding that is most strongly emphasized in the current manuscript is that the levels of catecholamines were elevated to dangerous levels in opioid-dependent individuals three days after they ceased opioid use. In our understanding, although similar effects have been reported in case reports and experimental model systems, this appears to be the first time such an increase has been observed in a clinical study. That said, the most highly competitive journals do publish some papers that present a new phenomenon without much further direct exploration, but in most fields, they mainly prioritize those that establish a comprehensive basis for the findings. Given the serious nature of the problem investigated in this study, we think that the findings could be of interest to a very wide audience of readers. We think that readers in the fields of psychiatry and psychopharmacology may be particularly interested in the findings related to buprenorphine and that researchers in addiction sciences may be particularly interested in the mechanistic aspects of addiction proposed.

*Nature*, the indicated target journal, is read by a broad audience and has previously published articles on related topics. Even so, in our understanding, at a fundamental level the conclusions seem to generally fit within our existing framework of understanding regarding opioid withdrawal, the corresponding effects on catecholamine levels, and the role of autonomic dysfunction. As this journal

primarily publishes basic research that represents a major breakthrough in our understanding, we are unsure whether this study would be seen as a priority for publication. You might nevertheless wish to submit to this journal or *Science*, particularly if you feel that we have underestimated the novelty of the main findings. In a similar vein, you may wish to consider submitting to *Nature Communications* or *Scientific Advances*, open-access options from the publishers of *Nature* and *Science*, respectively; these competitive journals also have broad scopes but regularly publish findings that will be of interest to specialists.

In our opinion, the following journals seem to be reasonable targets for submission:

- Should you wish to target researchers interested in the medication aspects of your topic, you may wish to consider journals such as *Psychopharmacology*. This journal publishes on a broad range of topics related to the mechanisms underlying the effects of drugs, including clinical studies involving human psychopharmacology. Additionally, this journal has previously published on the effects of buprenorphine on opioid-dependent individuals.
- Both *Addiction* and *Journal of Addiction Science* publish studies covering a wide range of topics related to addiction. Both journals reach a diverse audience of clinicians, researchers and policymakers and cover aspects of addiction including etiology, epidemiology, and clinical care and thus their scopes seem well aligned with the scope of this manuscript.
- Finally, if you wish to reach a broader audience, you may be interested in an open access journal that publishes medical research studies, such as *BMJ Open*, or one that publishes studies from all fields of science, such as *Scientific Reports* and *Plos One*. These journals publish a very wide range of papers as long as they are scientifically sound and do not base their decisions on the perceived importance of the findings, and they also have a reputation for reaching the publication stage relatively quickly.

### **GENERAL GUIDANCE ON PAPER STRUCTURE AND CONTENT**

In general, a paper communicates the scientific results in three stages: it establishes a central idea, it provides an argument, and it makes a point. This applies to the paper as a whole: the Introduction explains the background and rationale that leads to an aim, the evidence gathered in investigating this aim is presented in the Results, and the conclusion is established and discussed in the Discussion section. The same approach also applies to individual paragraphs: the sentences and their order should be crafted to establish a narrative with a coherent and logical flow. Ideas should be explicitly connected between sentences and paragraphs, for example by using suitable transitions.

**Title and Abstract:** Most people who encounter your paper will only read the Title, and many will stop at the Abstract. Therefore, to attract the desired target audience to the main paper, these sections should be concise and enticing, yet specific enough to clearly communicate what the paper is about. The Abstract should provide a concise and self-contained description of the most relevant previous understanding, the problem/question to be addressed in the paper, the overall approach and the most important results, the main conclusion, and a broader consideration of what the conclusions tell us or where they lead us next.

**Introduction:** The aim of the introductory paragraphs is to clearly and concisely establish the context of the main question that the paper is trying to answer, how the paper relates to previous research in the field, and why it is important – the ‘hook’ that shows the readers why they should care. Optionally, the Introduction can very briefly describe the methodology that is used and the rationale for choosing it, and the main conclusions.

**Methods:** The methodology should be coherent and self-contained, such that a competent person could repeat the study and reproduce the results by following the instructions given. This can be achieved either by citing existing papers or protocols in which aspects of the methods have been described in detail, or by giving explicit, in-text instructions. For some journals, very specific details can be moved to a supplementary section or appendix, so as to not disturb the overall flow of the paper.

**Results:** The purpose of the Results section is to present, in a logical order, the research data that are relevant to the central arguments of the paper. The results should be clear and concise, with important trends made clear to the reader and relevant statistical analysis accurately described. The figures and tables should be logical, clear and complete (labels, legends, units etc.). Captions should be as self-contained as is reasonable, ideally so that a reader can understand the main message of the figure/table without needing to read the paper in full.

**Discussion:** The Discussion aims to provide an analysis of the results and clear, scientifically sound conclusions that are firmly based on the data analysis. The Discussion should relate clearly to the main hypothesis/question posed in the Introduction – it should explain how the presented evidence substantiates the main claims of the paper, or if not, why not. The stated conclusions should not exceed, and the text should objectively state, the limitations of the study (without exaggerating these limitations so as to undermine the paper unnecessarily). The Discussion should highlight any need for additional research to resolve any contradictions or exceptions brought to light by the study.

**Concluding paragraphs:** Ideally, the end of the paper should not repeat what has already been said; instead, it should offer something new to the reader, for example explaining how the reported findings fit into the bigger picture (wider applicability, relevance to other fields/species) and/or what further research might address the unanswered questions or otherwise further our understanding.

**Cover letter:** The cover letter provides a direct line of communication with the journal editor to support them in any decision eventually to accept the manuscript for publication. It includes very brief contextual information if needed, then a brief and reasonably accessible description of the key findings, and finally a short explanation of why those findings would be of interest to that particular journal’s readers. Ideally, the main cover letter should be only about one page long, to ensure that the editor can easily identify the key points. Journals often also ask for information to support the publication process, such as ethics declarations and suggestions of peer reviewers to select or avoid.