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LETTER TO THE EDITOR

Response to “The Use of Non-Invasive Vagus Nerve Stimulation to Treat Respiratory Symptoms Associated with COVID-19: A Theoretical Hypothesis and Early Clinical Experience”

To the Editor:

Due to its noninvasive nature and ease of use, there is increasing interest for transcutaneous vagus nerve stimulation (tVNS) as a neuromodulation technique. However, like many emerging fields in medical science, tVNS is hampered by a proliferation of small-scale uninformative and underpowered studies. These studies typically report positive effects that remain unreplicated. Another potential point of concern is the device manufacturers' involvement in many of those studies, which further enhances the risk of a systematic bias in the literature (1). A recent case report published in *Neuromodulation* on effects of cervical tVNS on symptoms of COVID-19 (2) seems exemplary of both concerns, as further explained below. We believe it is important and timely to address these issues.

FINANCIAL INTERESTS

Financial conflicts of interest can lead to a systematic bias in the literature, as companies are incentivized to publish favorable results and draw more positive conclusions from their results (3,4). In the case of the recent report by Staats and colleagues, four of the authors own stocks in the company that produces the neuromodulator used in the study (electroCore, Inc.); three of the authors are actively employed by the company. A positive point is that these financial conflicts of interest are clearly mentioned in the article, but even then such conflict may threaten the objective nature of the research.

An additional concern may be that both the first and the senior author of the manuscript are members of the editorial board of *Neuromodulation*, with the senior author being its editor-in-chief. We assume and trust sufficient care was taken to prevent that the authors' position as members of the editorial board may unwittingly have smoothed the review process. To enhance transparency on this matter, the ethics guidelines described by *Wiley* might be helpful for this and future occasions. They indicate that “a short statement may be useful for any published article that lists editors or board members as authors to explain the process used to make the editorial decision” (5).

SCIENTIFIC SCRUTINY

The study by Staats and colleagues provides a case report on two patients who had been diagnosed with SARS-CoV-2. While the manuscript does not contain a description of how the researchers came into contact with the two patients, it seems clear that both patients were already familiar with the tVNS device and Case 2 had already used the device to treat his asthma-related complaints in the past. However, while neither patient was blind to treatment, there is no mention of potential expectancy biases in the manuscript.

Important details about the treatment are not provided, including which stimulation parameters had been used, how decisions regarding the stimulation procedure were made, and how symptom improvement was examined specifically. While the report mentions an unspecified “immediate and consistent symptom relief” and an improved ability to clear the lungs for patient 2, the report provides no indications to suggest that cervical tVNS had any treatment benefits for patient 1. Both patients recovered from their Covid-related symptoms, but it remains unclear whether tVNS had any effects on the speed of their recovery. From a scientific or clinical point of view, these case reports provide no new information about the feasibility or efficacy of tVNS as a treatment add-on for respiratory symptoms associated with COVID-19. The low informational value of the study, combined with the fact that it was written by employees of electroCore, makes this study seem more like a commercial rather than a scientific publication.

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Conflict of Interest: None.

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to <http://www.wiley.com/WileyCDA/Section/id-301854.html>

We would like to emphasize that we do not principally disagree with collaborations between researchers and industry. We do, however, urge researchers to be mindful of the importance of robust, slow science, and avoid bloating the scientific literature with studies that are uninformative, underpowered, or not pre-registered. Given that industry sponsorship can be considered as bias-inducing (3), researchers who are funded by the industry should place particular importance for ensuring high levels of transparency and scientific rigor. Reviewers and editors should in turn be extra mindful of their important role in safeguarding the scientific value and transparency of each submitted manuscript.

Authorship Statement

This letter was written by Andreas Burger and Martina D'Agostini. Prof. Ilse Van Diest (Health Psychology Group, KU Leuven) has contributed equally to writing this letter, but offered to relinquish authorship to ensure adherence to the editorial policy of *Neuromodulation*, which states that a letter to the editor may only include a maximum of two authors. For all intents and purposes, prof. Van Diest should be regarded as a co-author of this manuscript.

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