Review of: "The Concept of ME/CFS"

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Potential competing interests: No potential competing interests to declare.

In my opinion, this manuscript entitled *The Concept of ME/CFS* wrestles with the problems of defining ME/CFS: What is the precise nature of ME/CFS, how should we proceed with understanding its pathophysiology, and who should be involved in doing so?

In my opinion, the content of the article exceeds the title, and therefore the title should be revised to align with its content.

While I am in agreement with most of the content of this opinion piece, I find the article somewhat confusing. While the title of the article implies a global view of the subject, the content in most places appears to be U.K.-focused.

The article is well-timed as, in my opinion, the “concept” of ME/CFS is undergoing unprecedented change at this time: Long COVID demonstrates that a unique virus is not a requirement for ME/CFS to be produced. The 40-year search for that unique virus may now be halted. The National Academy of Medicine (U.S.) case definition of Long COVID is so focused on treatment that it has abandoned the need to demonstrate the previous infection of any virus and relies on the presence of patient symptoms only. Thus, the majority of ME/CFS patients satisfy NAM Long COVID case criteria and could and should avail themselves of the Long COVID treatment centers which may blossom should the Long COVID “Moonshot” Legislation pass in the U.S. (There are very few ME/CFS treatment centers in the U.S.)

If the article is intended to provide the global perspective, then it should include some of what is happening across the pond. If the article is intended to be U.K. or Europe-specific, it needs to include a bit more of what is happening in the U.K. and/or Europe.

The author does mention the unfortunate medical treatment that at least one patient has received at the hands of the NHS in the U.K. I know of this and many more unfortunate cases of ME/CFS patient mishandling by the NHS. Citing just one case doesn’t adequately describe the situation. In particular, I think the abuse of parents by the powers that be declaring children victims of Munchausen’s Syndrome By Proxy should be mentioned.

I offer the following specific criticisms with the intent of strengthening and improving the manuscript:

(1) The manuscript is one person’s opinion. The manuscript should be labeled as such, and the person’s credentials should be listed. (If the reader is being asked to read the opinion of one person, the reader should know the basis upon which the author is rendering his/her opinion.)

(2) The intent of the article needs to be articulated at the beginning. The intent I believe is expressed many paragraphs

into the manuscript: *There is more work to do to get the concept of ME/CFS as clear as it could be.*

(3) However, that intent is only part of the opinion expressed. The author, in my opinion, goes beyond the concept of ME/CFS and explores who should treat it. Is the title and the intent, therefore, inaccurate? If the author is attempting to increase the clarity of the concept of ME/CFS, he has not done so. If the intent of the author is to provoke a path forward which will increase the clarity of the concept of ME/CFS, he has not done so.

(4) Further down, I am led to believe that the manuscript is focused on the U.K*: What has come to public attention through the media in the UK in recent months is that alongside progress in scientific enquiry there has been a more or less total collapse of NHS services for people with ME/CFS.* After reading the entire manuscript, I am uncertain as to whether the manuscript is meant for an audience in the U.K. or if the author is citing an example from the U.K. If the audience is members of the U.K., this needs to be stated (to provide non-U.K. readers with perspective). If the audience is worldwide, then the author needs to state that he is drawing but one example from the U.K. Further, shortly before his death, Derek Phebe forwarded to me new NICE Guidelines concerning ME/CFS. Derek was very proud of his participation in creating these Guidelines. Have these Guidelines had no influence in the U.K.? Is the author's statement inaccurate?

(5) I disagree with the underscored portion of the author's following statement: *NICE also describes ME/CFS as a 'complex, multi-system, chronic medical condition'. 'Complex' and 'multisystem' are probably not helpful. 'Complex' tends to tacitly imply unspecified psychological factors, which just obscures things (and was not intended).* As a medical school physiology professor, we taught our students about multi-system illnesses and their complex nature. In teaching physiology in the United States, endocrinology is the last organ system in the course to be taught because the effect of hormones is on multi (many) systems. As an instructor of the U.S. Centers for Disease Control Chronic Fatigue Syndrome Course, given to physicians, we spoke of CFS as being complex and multi-system without mentioning or implying that such verbiage includes, "psychological factors."

(6) I agree with the author that *ME/CFS should not be considered a syndrome*, which the author defines as *a pattern of clinical symptoms and/or signs that suggest some common mediating process, even if that remains unknown.* I believe that the multiple studies indicating the strong overlap of symptoms of ME/CFS and Long COVID, coupled with the chapter recently published by Oxford University Press (https://academic.oup.com/book/58667/chapter-abstract/485344713?redirectedFrom=fulltext&login=false), strongly indicates that ME/CFS is frequently triggered by viral infection and, therefore, represents a pathological event or pathological events subsequent to the initiation of that infection. Because ME/CFS, in most cases, occurs subsequent to infection, it should not be considered a mere pattern of clinical symptoms and/or signs.

(7) I disagree with the author's statement: *Unfortunately, the descriptions of symptoms in accepted criteria for ME/CFS are not that precise and estimates of proportions of post-Covid cases who fit ME/CFS criteria are likely to be misleading*. The number of Long COVID cases far exceeds the number of ME/CFS cases at this point in time, and the focus is, therefore, reversed. The battle is now to have ME/CFS patients treated, and as the focus is now shifted to Long COVID, the ME/CFS patients will need to find care in Long COVID treatment centers (at least in the U.S.). Moreover, the

funding of clinical Long COVID research will far exceed that for ME/CFS. Therefore, the focus will be on Long COVID rather than ME/CFS, and the question to be asked is how does ME/CFS fit the Long COVID case criteria? In the United States, that question has been largely addressed by the National Academy of Medicine case definition of Long COVID, which is symptom-based and does not require the demonstration of a previous viral infection. Most ME/CFS patients satisfy the NAM Long COVID case definition. If this article is mainly focused on care in the U.K., then some mention of which case definition is being used by the NHS should be included, and what is the likelihood of a change in the case definition used in the post-Long COVID era?

I applaud the author's goal, but I do not think he has achieved it. I recommend refinement prior to publication.

I thank you for the opportunity to review this paper.