

## Reviewer's report

**Title:** Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution

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**Reviewer:** Susanne Merz

**Level of interest:** A paper of limited interest

**Advice on publication:** Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

1. Is the question posed by the authors new and well defined?

The question is new and is defined by the contents of the 1994 CFS criteria.

2. Are the methods appropriate and well described and are sufficient details provided to replicate the work?

The International Chronic Fatigue Syndrome Study Group formulated the 1994 CFS-criteria. It is therefore beyond doubt this group that should propose a revision of the CFS-criteria. The members' collective competence covers all relevant specialties.

The methods are well described and appropriate. The reasoning behind the proposed changes are clearly described.

3. Are the data sound and well controlled?

Compulsory revisions (a-d):

a) According to the CFS-criteria they work with, the authors should distinguish between chronic fatigue (CF) and chronic fatigue syndrome. The Study Group's goal of getting researchers to define CFS according to the current CDC-definition requires the Group's own terminology to be consistent and correct. But unfortunately, several times in the article, the term CFS is used where CF should stand, since the studies cited (for example refs. 11-13, 18-19, 23) didn't use the then current CFS-criteria (CDC 1994), or didn't use them completely. Studies that compare patients who have been recruited using different CFS definitions (c.f. article's ref. 6) can only shed light on the least

common denominator: namely; chronic fatigue, not chronic fatigue syndrome. A common problem in CFS research is that researchers try to apply results of research from patient groups recruited from one definition to patients who fulfill a different definition. The ignorance of the CFS-problem and CFS-research which the Study Group rightfully laments and the described "lack of consensus in the findings of many well-conducted studies" arises from the fact that many researchers do not realize that there are substantial differences between the different criteria that all use the name CFS. (See also 4b below).

I suggest that this be made clear in the article by rewriting the section "Background" so that the reader is made aware that the article's refs. 2-5 do NOT describe identical patient groups. (The article's ref. 2 requires several physical criteria. The article's ref. 4 requires not even subjective symptoms beyond chronic fatigue, whence these patients fail to fulfill CDC criteria for CFS). A good summary of the background of today's CFS-controversy is found in the article's ref. 22.

b) Much new understanding about differential diagnoses has accrued since 1994. The article's list of differential diagnoses is far from complete. Collections of additional differential diagnoses appear in the article's ref. 2 and my refs. 1 (pp. 4, 12-13), 2 (pp. 6-12), and 3 (p. 3284). It should be stressed that "The primary purpose of clinically evaluating a person with unexplained fatigue is to identify and treat any underlying and contributing factors" (article's ref. 5). In this context I have the following comments:

\* I question whether a lifelong disease like diabetes mellitus should be viewed as a temporary medical exclusion (p. 5).

\* In connection with temporary medical exclusions, it would be beneficial if the Study Group defined how long cured cancer permanently or temporarily excludes the diagnosis of CFS.

\* It is not more plausible that a BMI > 40 leads to chronic fatigue than that a BMI > 45 does. Rather, it is plausible that a BMI > 40 already leads to chronic fatigue (p. 5).

\* The sentence "However, these illnesses may resolve with little or no likelihood of recurrence" (p. 5) fits in better at the end of the same paragraph, where it would be clear that the sentence refers to patients that have been healthy for at least 5 years. In general, the illnesses described have a high risk of recurrence.

c) A revised version of the CFS-criteria should summarize new recommendations for CFS-work-up in an easily surveyed fashion. The paragraph on investigation of sleep disturbance (p. 10) should be complemented with recent understanding about clinically indicated tests (my ref. 4 p. 8. However, S-cortisol is NOT appropriate for excluding Addison's Disease!) Additional recommendations are found in my ref. 1, p. 110. Even microscopy of blood can give diagnostic hints. It would be desirable for the Study Group to take a position on the significance of a positive 2-5A-test (my ref. 5).

d) The review of the various instruments that measure fatigue, sleep disturbance, neurocognitive functioning, and pain (pp. 5-8) should be published in a separate article. This section does not fall under the article's theme "ambiguities in the 1994 CFS-definition". Since this review section should be reworked and lifted out, I have not reviewed all of the scales presented. But many of the scales which the article claims to be tested with CFS have actually been used on patients with CF, which should be corrected. A number of references in the review-section (according to my spot checks, for example, refs. 12, 13, 15, 23, 24) have typographical errors: usually due to incorrect author initials. A thorough review can include additional scales used in research on CF or CFS. Examples of scales not included in the Study Group's review section are listed in the article's ref. 5 and in my refs. 1 (p. 102), 6-8. In order for future research findings to be more comparable, it is essential that the Study Group come up with a recommendation. In that context I wish to mention a newly developed rating scale for fibromyalgia and CFS, the FibroFatigue Scale (my ref. 8).

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Compulsory revisions (a, b):

a) In connection with the Study Group's revision of the 1994 CFS-criteria, one should be aware of the risk of further confusion, since there already are so many CFS-definitions. It is therefore of utmost importance to present the revised criteria in an unambiguous and easily surveyed fashion. I recommend adding a summary of the complete, revised CFS-criteria (not just the changes) in the form of a diagnostic fill-in form. That would provide clinicians throughout the world with an easily surveyed and easily accessible common instrument for their work-up and diagnosis. That could mean a very valuable step toward a more homogenous selection of CFS-patients.

b) The Study Group should suggest how the revised criteria should be cited: for example, CFS/CDC 2003, so that they can be distinguished from CFS/CDC 1994, CFS/CDC 1988, CF/Oxford, etc.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

Compulsory revisions (a-c):

a) The section's content should be presented in a more easily surveyed fashion.

b) The article suggests that "The concept of 'exclusionary conditions' makes sense only in research settings....In the clinical setting, patients with exclusionary conditions may be diagnosed and managed as having CFS...." (p. 9). It is illogical that CFS in research settings should be a diagnosis of exclusion, but in clinical settings include the large number of known differential diagnoses. My ref. 9 introduces the concept of CF-explained for patients with CF in connection with a differential diagnosis. An alternative is to completely abandon the requirement that CFS be a diagnosis of exclusion and divide patients into one subgroup with unexplained CFS and one subgroup with explained CFS.

c) The 1994 CFS-criteria suggest subgrouping CFS-patients in order to obtain a more homogenous patient basis for research studies. The Study Group gives examples:

\* CFS subjects with different levels of disability (p. 6).

In order for research findings between different research groups to be comparable, it is essential for the Study Group to suggest ONE common rating scale: for example, the FibroFatigue Scale (my ref. 8). The Study Group should define the values for subgrouping. Even if these values are arbitrary, they are a prerequisite for making findings between different research groups comparable. (That would not prevent research groups from using additional scales that they find useful).

\* Individuals with apparently resolved medical conditions that otherwise meet the CFS definition vs. those without prior illness (Discussion, p. 9).

\* CFS-patients with vs. without somatization (Discussion, p. 9).

\* Patients with vs. without chronic widespread pain (p. 11).

I suggest that the Study Group define additional subgroups (and present them in a more easily surveyed fashion than the article currently does): for example,

\* Patients with infectious debut vs. patients with gradual debut

\* Patients with short illness duration vs. chronic illness (to be defined)

\* Patients who improve over time vs. patients who worsen (to be defined)

\* Patients with vs. without autoimmune manifestations

\* Patients with positive vs. negative 2-5A test (my ref. 5).

6. Do the title and abstract accurately convey what has been found?

Compulsory revisions:

Title: yes, under the condition that the section "Definition and Evaluation of Fatigue" (pp. 5-8) is removed (to form the basis of a separate publication). That would in turn require corresponding

changes in the sections "Results", "Background", and "Conclusion".

Abstract: The first sentence "Chronic fatigue syndrome....has no confirmatory physical signs...." should be complemented "...or CHARACTERISTIC laboratory abnormalities....". The same change is required in the first sentence, second paragraph on p. 3.

Discretionary revision:

Abstract: less about method and more about results.

7. Is the writing acceptable:

Compulsory revisions:

A few typographical errors should be corrected:

p. 5, first paragraph: a space is missing i the sentence "3) major conditions whose resolution...."

p. 9, sixth line from the bottom: a space is missing in the sentence "1994 case definition and...."

p. 9, fifth line from the bottom: "expet" should be "expert".

Discretionary revisions:

p. 1: Suzanne Vernon's email address is marked as a hyperlink. Is that intentional?

p. 9: first line in the section "Conclusion": "The intent of this article was....": "was" could be changed to "is".

## References

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- 3) Merz S. Chronic fatigue syndrome. More and more differential diagnoses suggest a new view of this syndrome. *Lakartidningen* 2002;99:3282-7.
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- 5) Suhadolnik RJ, Peterson DL, O'Brien K, Cheney PR, Herst CV, Reichenbach NL et al. Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome. *J Interferon Cytokine Res* 1997;17(7):377-85.
- 6) Karnofsky D, Abbelmann W, Craver L, Burchenal J. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer* 1948;1:634-666.
- 7) Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology* 1997;35(1):16-23.
- 8) Zachrisson O, Regland B, Jahreskog M, Kron M, Gottfries CG. A rating scale for fibromyalgia and chronic fatigue syndrome (the FibroFatigue scale). *Journal of Psychosomatic Research* 2002;52:501-509.
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## Competing interests:

None declared.