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: Niloofar Afari

Level of interest: A paper whose findings are important to those with closely related research interests

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

In this timely and necessary article, the authors address the ambiguities and shortcomings of the 1994 chronic fatigue syndrome (CFS) research case definition (Fukuda, 1994). The authors represent the International Chronic Fatigue Syndrome Study Group, comprised of experienced international investigators who met for a series of meetings to further refine the research case definition for CFS and offer recommendations for improving the precision of case ascertainment for research purposes. CFS is a diagnosis of exclusion without a physiological marker and its definition is based on expert consensus. As a result, it is essential to provide clear and consistent guidelines for the application of the definition so that research findings can become systematic and reproducible. The guidelines and clarifications provided in this article will be very important in standardizing the assessment of patients with CFS for research studies, without fully revising the 1994 case definition. Nonetheless, the article raises several issues that are outlined below. Hopefully, addressing these issues can further strengthen this valuable article.

Discretionary revisions:

1. The authors recommend the Checklist Individual Strength (CIS) to measure the presence and severity of fatigue. There is significant overlap between this instrument and the Multidimensional Fatigue Inventory (MFI; Smets, 1995), both in terms of instrument items and scoring and subscales. Like the CIS, the MFI is a well-validated instrument with a good track record of use in a number of different studies; it has been increasingly used in US studies of fatiguing illnesses. Thus, it might be useful to add the MFI as a recommended measure of fatigue, which would further aid in the comparability of findings from CFS studies.

2. The authors mention in the Discussion that a thorough evaluation of persons with a fatiguing
illness requires an assessment of medications and supplements that could contribute to fatigue, along with other factors and symptoms. A list of examples of medications or supplements that could contribute to fatigue and would therefore be potentially exclusionary for a research classification of CFS would be helpful.

3. As the authors suggest in the Discussion, there is little data in support of a specific cognitive dysfunction in CFS persons. Rather, the data point to a global but non-specific deficit, most notably in the areas of attention and information processing. Thus, it is not recommended that neuropsychological measurement be used to classify CFS research participants. In fact, given the number and breath of studies on cognitive functioning in CFS, it seems redundant to recommend continued traditional neuropsychological testing, even in the form of newly developed batteries (pages 7-8). Instead, the field could benefit from a shift to studies of functional MRI and other tools that could illuminate the brain-behavior relationship in CFS.

Compulsory revisions:

1. The authors recommend the composite International Diagnostic Instrument (CIDI) or the Structured Clinical Interview for DSM-IV Axis I (SCID) as reliable instruments for detecting psychiatric illness in CFS persons (both co-morbid and/or exclusionary). Both of these instruments have a long track record of use, however the CIDI has been widely used in large epidemiological studies and therefore allows for national comparisons of psychiatric prevalence rates, whereas the SCID is better suited for clinical studies. Additionally, because of the difference in how they are administered, the SCID and CIDI often do not produce comparable results. It would be valuable for the authors to provide a more detailed discussion of these instruments and perhaps make suggestions as to the type of studies where one would be more useful than the other.

2. The issue of the minor symptom criteria and their assessment is extremely important to the validity of the case definition and its consistent application. The authors recommend the use of the Somatic and Psychological Health Report (SPHERE) as a means to assess the occurrence, duration, and severity of fatigue and the eight additional symptoms. However, there are 2 main issues in assessing these symptoms with the SPHERE. First, as the authors point out, these symptoms were selected on the basis of consensus and were not identified empirically. The extremely high prevalence of somatization disorder in CFS persons and their report of a large number of somatic symptoms attributed to their illness would suggest that the list of 8 symptoms is not exhaustive or necessarily valid. Thus, empirically generating a list of somatic symptoms associated with unexplained persistent and debilitating chronic fatigue should be of high priority and would greatly enhance the case definition. It is not clear whether the SPHERE, an instrument originally designed to screen for depression and anxiety would be an adequate instrument for the empirical investigation of somatic symptoms associated with CFS. Additionally, the literature on the SPHERE is rather limited to the utility of 12 of 34 or 36 items in screening for mental disorders in primary care.

Second, as they are currently stated, the minor symptom criteria for CFS are of a somatic nature (as opposed to psychiatric). With increasing evidence that prolonged or chronic fatigue can be differentiated from depression and anxiety and may be genetically distinct, it does not appear necessary to use a psychiatric screening tool to assess for the somatic symptoms associated with CFS. In a comprehensive evaluation of CFS persons in a research setting, the CIDI or SCID would provide more than adequate information about psychiatric symptoms/diagnoses and if necessary, another measure could be added to assess co-morbid psychological distress (e.g., GHQ, BSI, etc.). However, a distinct and somatically focused instrument or set of measures is necessary to evaluate the 8 symptoms in the case definition and perhaps additional symptoms that are commonly attributed to chronic fatigue or CFS. A detailed discussion of the rationale for recommending the SPHERE and the assumptions about symptoms associated with CFS would greatly enhance the manuscript.
**Competing interests:**

None declared.