PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Case definitions for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) - A systematic review
AUTHORS	Brurberg, Kjetil; Fønhus, Marita; Larun, Lillebeth; Flottorp, Signe; Malterud, Kirsti

VERSION 1 - REVIEW

REVIEWER	Jos WM van der Meer Radboud University Medical Centre, Nijmegen THe Netherlands
REVIEW RETURNED	16-Oct-2013

GENERAL COMMENTS	This paper reports on a very well executed and critical investigation. The investigation was performed with an open mind and the conclusions are strong. It is well written and readable. The authors draw a number of highly relevant conclusions. My comments are only minor and few. 1. It is an important question why we need diagnostic criteria. Do we need them for research (epidemiology, clinical trials) or do we need them for the individual patient to make a diagnosis (and for insurance purposes)? For research, the immediate question is do we want sensitive criteria (we do not want to miss any possible patient), or do we want specific criteria (we may miss some patients, but those that qualify are definite cases)? This problem is discussed pretty well in the Discussion section under 'Broad or narrow definitions'. To my mind this comes a bit late. In fact, it could be alluded to already in the Introduction. 2. The authors point out that there is a difference between questionnaire responses and clinical interviews (p12). This point may be put forward a bit more precise. If patients are given a standardized questionnaire, more symptoms will be scored than when they are asked to report their symptoms spontaneously. Swanink et al (J Int Med 1995; 237:499-506) have reported that the first method yields considerably more symptoms than using the second method. This is very relevant, but the way the data are gathered is rarely reported in the methodology sections of papers. 3. In the Introduction (line 4), the authors mention autoimmune dysfunction, while referring to the Fluge paper. The term autoimmune should not be loosely applied: the evidence for auto-aggressive T or B cells is meagre, and if anything, the particular reference is only supportive for an immunological pathogenesis. The structural abnormalities in the brain (loss of grey matter), as originally put forward by Okada et al (BMC. Neurol. 2004), and by De Lange et al (Neuroimage, 2005) have been demonstrated to be reproducible. Hence these are better references on page 4, line 9 than the ones used (4, 15).

REVIEWER	Sonya Marshall-Gradisnik Griffith Health Institute National Centre for Neuroimmunology and Emerging Diseases Griffith University, Parklands, Gold Coast, QLD Australia
REVIEW RETURNED	28-Oct-2013

GENERAL COMMENTS	Minor Comments: Methods and Materials: first sentence needs to be reworded "But we did not" Major comments: Page 7: Independent application: Sentence "most of the patients" This description of the use of Fukuda and the Canadian Definition, needs to be completely re-worded as it does not highlight the Canadian definition is more specific for symptoms than the Fukuda. The latter is non-specific and as such this is the reason for only 47% being positive. Hence the authors needs to further outline this in this section as currently it not truly representing this The authors needs to reword and restructure sentences in discussion commencing with "According to our view" Again the structure of this sentence states the author are determining trying to focus on defining more case definition of CFS. In this instance the ICC definition utilised more specific immunological, neurological and endocrinological data with functional assessments. The use of such a criteria is designed to assist to clearly define a case definition for CFS/ME. Hence these sentences by the authors needs considerable rewording Conclusions: The authors clearly are not aware there is no treatment for CFS/ME as there is no pathological mechanism documented for this illness. Irrespective of the findings by Fluge et al there is still no founded treatment and for this reason the sentence starting "Priority should be given..." needs to be removed as there is no proven treatment. there are no clinical trials.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: This paper reports on a very well executed and critical investigation. The investigation was performed with an open mind and the conclusions are strong. It is well written and readable. The authors draw a number of highly relevant conclusions.

Our response: Thank you for this encouraging feedback.

Reviewer 1: It is an important question why we need diagnostic criteria. Do we need them for research (epidemiology, clinical trials) or do we need them for the individual patient to make a diagnosis (and for insurance purposes)? For research, the immediate question is do we want sensitive criteria (we do not want to miss any possible patient), or do we want specific criteria (we may miss some patients, but those that qualify are definite cases)? This problem is discussed pretty well in the Discussion section under 'Broad or narrow definitions'. To my mind this comes a bit late. In fact, it could be alluded to already in the Introduction.

Our response: We agree, and have added a new paragraph in the “Introduction” about broad versus narrow criteria to meet this request.

Reviewer 1: The authors point out that there is a difference between questionnaire responses and clinical interviews (p12). This point may be put forward a bit more precise. If patients are given a standardized questionnaire, more symptoms will be scored than when they are asked to report their symptoms spontaneously. Swanink et al (J Int Med 1995; 237:499-506) have reported that the first method yields considerably more symptoms than using the second method. This is very relevant, but the way the data are gathered is rarely reported in the methodology sections of papers

Our response: We appreciate this suggestion, and we have added a reference to Swanink et al in "Discussion". Moreover, we have added a couple of sentences to delineate our point more precisely which is shown in bold in the manuscript

Reviewer 1: In the Introduction (line 4), the authors mention autoimmune dysfunction, while referring to the luge paper. The term autoimmune should not be loosely applied: the evidence for auto-aggressive T or B cells is meagre, and if anything, the particular reference is only supportive for an immunological pathogenesis. The structural abnormalities in the brain (loss of grey matter), as originally put forward by Okada et al (BMC. Neurol. 2004), and by De Lange et al (Neuroimage, 2005) have been demonstrated to be reproducible. Hence these are better references on page 4, line 9 than the ones used (4, 15).
Our response: We agree, and have updated our references accordingly

Reviewer 2: Methods and Materials: first sentence needs to be reworded "But we did not"

Our response: We have changed the wording

Reviewer 2: Page 7: Independent application: Sentence "most of the patients" This description of the use of Fukuda and the Canadian Definition, needs to be completely re-worded as it does not highlight the Canadian definition is more specific for symptoms than the Fukuda. The latter is non-specific and as such this is the reason for only 47% being positive. Hence the authors needs to further outline this in this section as currently it not truly representing this

Our response: We understand the reviewer's point of view, and agree that the Canadian criteria were developed to achieve a case definition that is more specific for symptoms than Fukuda. This may very well turn out to be the case, but in our review we aim not to go into details in the specific design of various case definitions. We rather emphasize the need for robust validation studies before concluding about hypothesized differences between various case definitions. As demonstrated in our review, we still lack robust evidence to conclude firmly about the difference between the two case definitions. If we state that the Canadian definition is more specific than Fukuda we feel that we preceed the evidence, and therefore we find it hard to comply with this request.

Reviewer 2: The authors needs to reword and restructure sentences in discussion commencing with "According to our view" Again the structure of this sentence states the author are determining trying to focus on defining more case definition of CFS. In this instance the ICC definition utilised more specific immunological, neurological and endocrinological data with functional assessments. The use of such a criteria is designed to assist to clearly define a case definition for CFS/ME. Hence these sentences by the authors needs considerable rewording

Our response: As one of the authors of the ICC definition we are sure that the reviewer possesses more detailed knowledge about these criteria than we do. Again, however, we urge the need for rigorous validation studies to confirm hypothesized differences between various case definitions before we conclude. Furthermore, as discussed in the paragraph "The utility of case definitions and diagnoses" we believe that narrowing case definitions is primarily valuable if they can be used to

predict differences in prognosis or expected effects of therapy

Reviewer 2: Conclusions: The authors clearly are not aware there is no treatment for CFS/ME as there is no pathological mechanism documented for this illness. Irrespective of the findings by Fluge et al there is still no founded treatment and for this reason the sentence starting "Priority should be given..." needs to be removed as there is no proven treatment. there are no clinical trials.

Our response: We agree with the reviewer that no documented pathological mechanism for CFS/ME exists, though we disagree with the view that unknown pathological mechanisms implies that there is no treatment for CFS/ME. Lack of a definite curative treatment does not exclude the existence of effective symptom management. In fact, several high quality trials have shown that CBT and GET may improve fatigue and physical functioning. As we discuss on page 13, one of these trials compared the effectiveness of GET and CBT between a CFS population and a ME population (London ME) and found comparable results.

VERSION 2 – REVIEW

REVIEWER	Jos WM van der Meer Dept of Medicine Radboud University Medical Centre Nijmegen Netherlands
REVIEW RETURNED	29-Dec-2013

- The reviewer completed the checklist but made no further comments.

REVIEWER	Sonya Marshall-Gradisnik Griffith University Griffith Health Institute National Centre for Neuroimmunology and Emerging Diseases Queensland Australia
REVIEW RETURNED	14-Jan-2014

- The reviewer completed the checklist but made no further comments.