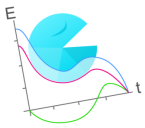


# M.E. Analysis – Evaluating the results of the PACE study

a project supported by Phoenix Rising

## 1. Future studies should not use the Oxford Criteria (further details)

**A rose by any other name ... or fifty flowers named rose?**

*How failure to perform differential diagnosis has marginalized an entire population of seriously ill and misdiagnosed patients and confused the research and medical communities for decades.*

**Official US Definiton: usual diagnostic definition internationally, research definition**

The Fukuda definition requires profound debilitating fatigue, lasting or recurring for at least 6 months, and that is of new or definite onset, is not from ongoing exertion and does not resolve with rest, and that this fatigue is specifically defined as "mental and physical exhaustion, which differs from somnolence or lack of motivation". (Given the typical usages of the words, weakness probably would have been a better choice for what they describe than fatigue.) Additionally, there must be at least four items from the following list which must correlate with the disease (i.e. they must not have been present beforehand):

- debilitating problems with short-term memory or concentration;
- sore throat;
- tender cervical or axillary lymph nodes;
- muscle pain; multijoint pain without swelling or redness;
- headaches of a new type, pattern, or severity (including migraines);
- unrefreshing sleep;
- postexertional malaise (weakness and symptom flare, usually including dyspnea and flulike symptoms; pathologically long recovery of days, weeks, or more; triggered by physical and/or mental activity, which can be even trivial activity; the onset of this response may be delayed)

Major depressive disorders and other psychiatric-classified disorders which could result in serious fatigue are considered exclusionary, as are other medical-classified disorders which could explain the signs and symptoms, except fibromyalgia since it does not typically follow an infectious onset. If the possibly explanatory condition is fully treated, yet symptoms remain, or if symptoms are not explained by the other condition, the other condition is not supposed to be considered explanatory and a diagnosis of CFS is presumed (however, this is not generally how the exclusions are typically used, especially since CFS is often mistakenly taken to be a somatoform disorder). This inclusion was designed for research, but is also used to make clinical diagnosis.

Although the rubric does make a serious attempt at differential diagnosis, there is no requirement for any feature specific for ME/CFS, while the symptoms overlap with major depressive disorder (MDD) and other diseases, and it is thought that the Fukuda population contains some missed primary depression even in fairly good conditions. There is an ideological bias (without supporting evidence) among some researchers that it is unnecessary to differentiate between primary depression and CFS because CFS is a form of affective, maladjustment, hypochondriac, or somatoform disorder (see, for example, a discussion of how this came about and why it is incorrect in Jason et al. "Politics, Science, and the Emergence of a New Disease: the Case of Chronic Fatigue Syndrome"), and among these researchers, a Fukuda-defined population will have a high percentage of primary affective disorders, which the definition allows if one ignores those exclusions. The PACE study used the Fukuda for subgrouping only after pre-screening the entire enrolled population by use of Oxford inclusion. This raises the likelihood that those who met Fukuda in the PACE subgroups did so via symptomology inconsistent with a neurological disorder (this is how the World Health Organization classifies ME/CFS in G93.3 on the basis of the work of physicians like A Melvin Ramsay; notably, findings in early CFS definition cohorts include MRI abnormalities).

It is also possible that the Fukuda population contains several different types of post-infectious and chronic infectious disease, some of which resolve after a few years and some of which do not resolve. In addition, the population is agreed to be heterogeneous as to multiple characteristics, and there are likely to be additional factors which contribute to this heterogeneity which are not presently understood. It should be noted that the Fukuda article specifically directs research to be stratified according to several factors. This is very rarely done. Although everyone admits the heterogeneity, few seem to do much about it. Rather than stratify the group, the trend has been to broaden it further, still with no subgroups or stratification.

**Common British Definition: research definition, diagnostic definition in Britain**

A commonly-used definition in Britain is the Oxford Criteria. The only required symptom is severe disabling fatigue of new or definite onset, lasting at least six months; the fatigue of this definition may be related to lack of motivation and is permitted to be psychiatric in nature. Other permitted (but not diagnostic-contributory) symptoms include muscle pain, and mood and sleep disturbances. For research purposes, sometimes no clinically verifiable abnormalities (muscle twitches, bloodwork differences even if not clinically significant, etc.) are allowed, and sometimes abnormalities which are considered minor or of secondary significance are permitted. In clinical practice, persons diagnosed with or suspected to have CFS in Britain often have had a minimum of clinical investigations. There is a hypothesis, despite a lack of evidence, that too many investigations will encourage the patient in an abnormal illness belief and thereby impede recovery.

In effect, the use of the Oxford criteria is to give a diagnosis on the basis of a failure to find an alternative diagnosis. It focuses on fatigue which is a consequence of many chronic illnesses, and is found to a lesser extent in many healthy people, but treats fatigue as if it were a primary defining feature. By grouping together a mixture of different conditions, both medical-classified and psychiatric-classified disorders, it opens the way for a variety of treatments or therapies (including GET and CBT) to produce small average overall improvements simply by being helpful to a subset or by having a nonspecific effect on a variety of unrelated diseases (CBT, for instance, is used with moderate effect to impact the well-being of patients with diseases as diverse as cancer, multiple sclerosis, primary anxiety, and chronic obstructive pulmonary disease).

The conclusions to this proposed definition in 1990 were "*The contributors hope that these guidelines will provide a basis for fruitful research studies, and for inter-disciplinary collaboration essential to this field of research. The guidelines are preliminary and will undoubtedly require further refinement and revision. The authors would welcome comments and suggestions*" but the definition has remained as it is, in general use in the UK for the last 20 years, although its usage is less common now than it was in the 90s.

**Unofficial US Research Inclusion Criteria, often described as Fukuda**

A new rubric from the CDC, the CDC Empirical Definition, colloquially known as the Reeves criteria, is neither empirical nor a definition. Its objective is to operationalize the Fukuda criteria, but the actual effect is to destroy the requirements of Fukuda. Instead of requiring four diagnostic-contributory symptoms which are continuous or recurrent over the previous six months and associated with the disease, one still must endorse four items, but needs only to score a total of 25 points in symptoms over the single previous month (frequency x severity: any one item can score up to 16), and none of these need to be associated with the disease. This means that a form of post-viral fatigue which subsequently resolved as normal, a particularly long case of mono or other self-resolving form of post-viral fatigue, a case of unrelated back pain or of post-nasal drip, all could make a substantial contribution to the diagnosis. Instead of requiring a pathological reduction in activities, CDC Empirical considers a full quartile of the general population to qualify.

With this rubric, depression is considered to meet the Fukuda criteria, although Fukuda itself actually excludes primary depressive conditions that could be causing a serious level of fatigue. Jason has shown that 38% of patients with major depressive disorder can be misdiagnosed with CFS by use of this rubric. He has also argued that the reported incidence of CFS increased 10-fold coincidentally with the introduction of this rubric, and that the new prevalence of Empiric-CFS coincidentally approximates the prevalence of mood disorders (page 121).

Research using the CDC Empirical inclusion will say they used the CDC Fukuda definition. One has to check the full text to see where they have cited Reeves' 2005 paper.

**Other Definitions**

There is the Canadian definition which is more specific for the neurological and immune disease of myalgic encephalomyelitis (ME), classified by the WHO as a neurological condition (G93.3), and is closer to the disease that the first CFS definition was attempting to describe (this disease is also known as Epidemic Neuromyasthenia). There are also historic definitions of ME, such as the Ramsay definition, under which there is a large body of research and clinical data available which is largely ignored. These are also included in the second report by Jason mentioned above.

For a historical list of research literature and definitions, there is a wiki under preparation that may be useful (see the online page for links).

**Discussion**

Using the Fukuda definition, and occasionally the Canadian criteria, clinically useful biological information about ME/CFS is available and a reasonable amount of this has been verified by replication studies.

The Fukuda definition is polythetic (select any 4 from a list of criteria) and does not necessarily require the characteristic traits of ME, so "dilutes" any patient study sample. However, the Fukuda is the more specific of the two definitions in common use today: the Fukuda and the Oxford. Current treatment policies are based upon the average improvements found in studies using these two definitions, but this means that they can make recommendations based upon a wider patient population that are inappropriate to a more specific patient population being treated.