The Role of Case Definitions in Myalgic Encephalomyelitis and Chronic Fatigue Syndrome

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Case definitions are essential for any disease, both in terms of reliability identifying those that are diagnosed and those that are not diagnosed. Myalgic Encephalomyelitis and Chronic Fatigue Syndrome. There have been a number of different criteria proposed for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome, and a recent name change has been proposed by the Institute of Medicine (IOM) in 2015. It is critical to develop a consensus on a clinical and research case definition. Two studies have been conducted at DePaul University and they are reviewed in this article. Significant reliability issues were found for the recent IOM recommendations, and implications of these findings are discussed.

Investigators in Europe were among the first to research and study Myalgic Encephalomyelitis (ME) (Ramsay, 1986; Ramsay, 1988). Ramsay (1988) described the following distinct features of the illness: (1) muscle fatigability after minimal exertion and a delay in the restoration of muscle power; (2) cerebral dysfunction, and (3) impaired circulation. He also emphasized daily variation in symptoms and physical findings and the propensity for the illness to become chronic.

Unfortunately, individuals with ME and Chronic Fatigue Syndrome (CFS) often experience stigma. In support of this, in one study, 95% of individuals seeking medical treatment for ME and CFS reported feelings of estrangement (Green, Romei, & Natelson 1999). Another survey of healthcare providers found that 20% agreed with the statement, "I believe that CFS is all in a patient's head" (Brimmer, Fridinger, Lin, & Reeves, 2010). In addition, thousands of patients with ME and CFS cannot find a single knowledgeable and sympathetic physician to care for them (Tidmore, Jason, Chapo-Kroger, So, Brown, & Silverman, 2015).

It might be possible that this stigma and lack of understanding is in part due to problems with the case definitions. Case definitions are a set of rules that allows investigators and clinicians to determine who has and who does not have an illness, and as

such, they are the foundations for studying any illness. In a sense, case definitions are like a stack of cards. At the bottom row of cards, you need to establish a firm foundation, which is where the case definition begins. If the case definition is not reliable and valid, or in our analogy - if the foundation of cards is not study - then everything built on top becomes shaky and potentially problematic for the scientific enterprise, including issues involving the etiology, epidemiology, and treatment of the illness.

There are a number of problems involving the reliability of case definitions. Subject, occasion, and information variance accounts for only a small portion of diagnostic reliability (Jason, & Choi, 2008) and criterion variance accounts for the largest source of diagnostic unreliability (Spitzer, Endicott, & Robins, 1978). These are the differences in the formal inclusion and exclusion criteria to classify patients' data into diagnostic categories. Criterion variance occurs when operationally explicit criteria do not exist for diagnostic categories. If ambiguities in case definitions occur, investigators might select samples of patients who are different on fundamental aspects of this illness, and is an impediment to replicating findings across different laboratories.

If investigators in different settings select heterogeneous samples, these investigators will have difficulty replicating the results (Jason, Sunnquist et al., 2015). At the present time, we have what is called a consensus based case definition for CFS. The Fukuda et al. (1994) case definition was established by an international working group that published the criteria, and for the past 20 years, investigators around the world have used these criteria. Patients that meet these criteria are required to experience chronic fatigue and the concurrent occurrence of at least four of eight other symptoms. The symptoms are as follows: sore throat, tender cervical or axillary lymph nodes, muscle pain, multiple joint pain without joint swelling or redness, headaches of a new type patter or severity, unrefreshing sleep, post exertional malaise lasting more than twenty-four hours and persistent or recurring impairment in short term memory or concentration. The first five symptoms vary within the general population but the last three symptoms (unrefreshing sleep, post exertional malaise lasting more than twenty-four hours and persistent or recurring impairment in short term memory or concentration) are the fundamental core aspects of this illness. Because these criteria require only four symptoms out of a possible eight, critical CFS symptoms, such as unrefreshing sleep, post-exertional malaise or memory and concentration problems, are not required for a patient to receive a diagnosis of CFS.

In Chicago, researchers at DePaul University conducted a community-based epidemiologic study (Jason et al., 1999) using the Fukuda criteria. We found that about 4% of the population experiences six or more months of fatigue, that is about 1 out of 20 people have this symptom. About half those people (54 % of that 4%) had had a medical or psychiatric explana-

tion for their fatigue (e.g., melancholic depression, cancer, psychotic disorders). About 27% of this group of fatigued individuals did not meet the Fukuda et al. (1994) criteria for CFS. That means that the individuals did not have enough symptoms (at least four out of eight) to meet the criteria. However, 19% of the fatigued group did meet these Fukuda et al. (1994) criteria. This suggests that about .42% of the population in the United States, and possibly in Sweden, has this illness. What that means is out of every 200 people, one person would have the illness.

In the research the DePaul investigators engaged in during the 1990s (Jason et al., 1999), they found that people who had Major Depressive Disorders (MDD) have many of the Fukuda et al. (1994) symptoms. Symptoms of depression often include chronic fatigue and multiple somatic symptoms, including unrefreshing sleep, joint pain, muscle pain and impairment in concentration. MDD is one of the more prevalent psychiatric disorders, occurring in about 2.3% of the population. It is very important for people who have a solely psychiatric illness, like MDD, not to be inappropriately classified as CFS.

Because of the criticisms of Fukuda et al. (1994) criteria, such as not requiring cardinal CFS symptoms such as post-exertional malaise, and memory and concentration problems, the Canadian ME/CFS clinical criteria (Carruthers et al., 2003) was developed. This criterion requires the cardinal symptoms to occur (such as post-exertional malaise). The Canadian criterion has been more frequently employed over the last 10-12 years. The criteria requires the following symptoms: post-exertional malaise, unrefreshing sleep, pain (significant degree arthralgia and/or myalgia) without inflammatory response joint swelling or redness, two or more neurocognitive manifestations and at least one symptom from two of the following categories: Autonomic manifestations (light headaches), neuroendocrine manifestations (recurrent feelings of feverishness), and immune manifestations (recurrent sore throats).

A number of years later, the ME International Consensus Criteria (ME-ICC) developed (Carruthers et al., 2011). To meet ME criteria, symptom severity impact must result in a 50% or greater reduction of a patient's premorbid activity level for a diagnosis and eight symptoms, divided within the following four areas: Post-Exertional Neuroimmune Exhaustion, Neurological Impairment (3 symptoms), Immune, Gastro-intestinal and Genitourinary Impairments (3 symptoms) and Energy Production/Transportation Impairments. Whereas the Fukuda et al. (1994) CFS criteria required at least 4 symptoms, the Canadian ME/CFS clinical criteria (Carruthers et al., 2003) required seven symptoms, and the newer ME-ICC criteria (Carruthers et al., 2011) required eight symptoms. Unfortunately, later work with factor analysis with very large samples has not come up with these areas (Brown & Jason, 2014). The other potential problem is that increasing the number of symptoms increases the probability of identifying people

with psychosomatic issues.

In the spring of 2015, the Institute of Medicine (IOM, 2015) recommended changing the name of ME and CFS to Systemic Exercise Intolerance Disease (SEID), as well as proposed a new clinical case criterion. This has been a widely distributed set of recommendations. Also, in the spring of 2015, Lisa Petrison from Paradigm Change conducted a patient survey of 1,147 patients (Petrison, 2015) and found that the majority of respondents expressed negative opinions about the proposed name (SEID), the proposed naming process, and about the idea of the government using the proposed name. It is very possible that this survey will provide federal officials with important feedback about significant implications of changing the CFS name to SEID.

The IOM (2015) also made recommendations regarding a new clinical case criteria, involving the following four symptoms: substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, education, social or personal activities, post-exertional malaise, unrefreshing sleep, and at least one of the two following symptoms: cognitive impairment or orthostatic intolerance. These four symptoms for the most part are things that a number of factor analytical studies have found (Brown & Jason, 2014). While studies have found cognitive impairment in patients, orthostatic intolerance tends to occur less frequently (Jason, Sunnquist, et al., 2015). According to the IOM, if a patient has these four domains, the new clinical criteria would be met. However, the core IOM symptoms are not unique to SEID, as other illnesses have comparable symptoms (e.g., cancer, Hashimoto, lupus, chronic heart failure, multiple sclerosis, etc.).

The DePaul research group has published two articles in the last six months where the IOM clinical criteria were compared to other case definitions, including the Canadian criteria, the Fukuda criteria, the ME-ICC criteria, and the Ramsay criteria. One study involved seven hundred and ninety-six patients from the USA, Great Britain, and Norway, and patients had completed the DePaul Symptom Questionnaire (Jason, Sunnquist, Brown, Newton, Strand, & Vernon, 2015). Findings indicated that the IOM criteria identified 88% of participants in the samples analyzed, which is comparable to the 92% that met the Fukuda et al. (1994) criteria. The recently developed IOM (2015) criteria appears to identify a group comparable in size to the Fukuda et al. criteria, but these results came from clinically based samples. In addition, the IOM and Fukuda criteria would identify a larger group of patients than would meet the Canadian ME/CFS and ME-ICC criteria (Jason, Sunnquist, Brown, McManimen, & Furst, 2015).

In study two (Jason, Sunnquist, Kot, & Brown, 2015), the DePaul University group looked at what occurred regarding the issue of exclusionary illnesses with the IOM (2015) recommendations. Four different data sets were examined, and one was from a community-based epidemiology study, which went beyond more clinic

and tertiary care type settings. In that study, because participants were not self-selected individuals, we found the IOM's new clinical criteria would increase prevalence rates by 2.8 times. For example, 47% of those with Melancholic Depression met the IOM criteria. In addition, for those with a medical reason for their fatigue, 48% met IOM criteria. The authors concluded that the IOM criteria would identify a larger group of people from the general population as meeting this criterion.

There are currently multiple case definitions and each has different criteria. For moving the field forward, it is of importance to better operationalize each of the current criteria to reduce criterion variance, to compare and contrast current criteria, to use more sophisticated analytic structures to determine critical dimensions of each case definition, and to consider whether a research criteria might identify a more homogenous group than clinical case criteria. It is critical to develop a consensus on one research case definition, and then use it internationally.

Because the term SEID has not been endorsed for these IOM criteria, there is a need to find a name that might appeal to larger segments of the patient and scientific audience. One possibility for a clinical criterion is the term Neuroendocrine Dysfunction Syndrome, which had been recommended by the patient inspired Name Change workgroup over a decade ago to replace CFS. A research criterion based on Myalgic Encephalomyelitis as defined by Ramsay (1988) may help to identify a smaller group of patients with more functional impairment. Another possibility is to classify patients into the following categories: patients with fatigue and exclusionary psychiatric or medical illness; patients who meet IOM criteria, but who do not have psychiatric or medical exclusions; and patients who meet research criteria (Jason, McManimen, Sunnquist, Brown, Furst, Newton, & Strand, 2016). It is possible that those that do not meet the three criteria above could be classified as having chronic fatigue, which is the most general category, and represents those with six or more months of fatigue. In addition, it is of importance to have structured clinical interviews so one could determine whether a symptom is met or not, and whether the interview questions are asked in a similar way.

In summary, the broader IOM criteria, or some version of it, could be used for clinical purposes whereas a more restrictive ME criteria could be used for research purposes. Some scientists might prefer to consider the clinical versus research grouping a matter of severity rather than categorical differences, but such a classification system has the potential to clarify discrepant findings from epidemiologic, etiologic, and treatment studies. Developing a consensus for clinical and research criteria, as well as operationalizing such criteria with reliable questionnaires, is a high priority area for this field. Ultimately, decisions need to be made regarding the names and criteria for this illness. The vetting process needs to be open,

inclusive, and transparent, with scientists, clinicians, government officials, and patient groups involved in these deliberations.

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