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## Reflections on the Institute of Medicine's systemic exertion intolerance disease

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### Abstract

The Institute of Medicine (IOM) in the United States has recently proposed that the term systemic exertion intolerance disease (SEID) replace chronic fatigue syndrome. In addition, the IOM proposed a new case definition for SEID, which includes substantial reductions or impairments in the ability to engage in pre-illness activities, unrefreshing sleep, postexertional malaise, and either cognitive impairment or orthostatic intolerance. Unfortunately, these recommendations for a name change were not vetted with patient and professional audiences, and the new criteria were not evaluated with data sets of patients and controls. A recent poll suggests that the majority of patients reject this new name. In addition, studies have found that prevalence rates will dramatically increase with the new criteria, particularly due to the ambiguity revolving around exclusionary illnesses. Findings suggest that the new criteria select more patients who have less impairment and fewer symptoms than several other criteria. The implications of these findings are discussed in the current review.

### Keywords

case definition; systemic exertion intolerance disease; chronic fatigue syndrome; myalgic encephalomyelitis

### Introduction

A new name for chronic fatigue syndrome (CFS) and a new clinical case definition have been proposed by the Institute of Medicine (IOM)<sup>1</sup> in the United States. The new name is systemic exertion intolerance disease, and the new case definition requires the following 4 symptoms: substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities; postexertional malaise; unrefreshing sleep; and at least one of the 2 following symptoms: cognitive impairment or orthostatic intolerance. In addition to proposing a new case definition and a new name, the IOM<sup>1</sup> report provided a review of the literature and offered a number of recommendations

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that have received considerable attention from the scientific community. For example, Ganiats<sup>2</sup> stated that this report clearly shows that the disease has a physiological basis, and Komaroff<sup>3</sup> commented that the report provides evidence that patients have neurological and immunological impairments. Clearly, these types of high-profile commentaries help solidify the serious nature of this illness and build support for future investigations to better understand and treat this disease. In general, the IOM conclusions were well justified regarding depicting this illness as serious, emphasizing the identification of fundamental symptoms, and making recommendations regarding the need for more funding.

These new diagnostic criteria were proposed to replace the previous CFS criteria (by Fukuda et al.<sup>4</sup>) that require 4 symptoms out of the possible 8. Because of the polythetic nature of these criteria, some patients could meet criteria without experiencing cardinal symptoms of the illness, such as postexertional malaise, memory and concentration problems, or unrefreshing sleep. There are a number of possible unwitting consequences of not requiring fundamental symptoms within the Fukuda et al.<sup>4</sup> case definition, including a wide variability in CFS prevalence rates (0.004% to 0.0087%, 0.24%, 0.42%, and 2.54%).<sup>5-8</sup> The IOM,<sup>1</sup> as well as the larger scientific community, felt that new diagnostic criteria were needed to increase the probability that individuals included in samples had the same underlying illness. Clearly, issues concerning reliability of clinical diagnosis are complex and have important research and practical implications. For example, if investigators in different settings select heterogeneous samples, these investigators will have difficulty replicating the results. An inability to replicate findings interferes with the search for biological markers and effective treatments.

Over the past 20 years, 2 other sets of diagnostic criteria have been proposed that were more specific in requiring core symptoms: the Canadian Clinical Criteria for Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS)<sup>9</sup> and the International Consensus Criteria for Myalgic Encephalomyelitis (ME-ICC).<sup>10</sup> Rather than 4 symptoms required by the Fukuda et al.<sup>4</sup> CFS criteria, the ME/CFS criteria<sup>9</sup> required 7 symptoms, whereas the ME-ICC criteria<sup>10</sup> required 8 symptoms. Unfortunately, with the increase of symptoms from 4 to 7 or 8, criteria could identify individuals with higher rates of psychiatric comorbidity.<sup>11</sup>

The Fukuda et al.<sup>4</sup> criteria have been the most widely used criteria both in the United States and internationally. It should be noted that the Fukuda et al.<sup>4</sup> case definitions excluded a variety of medical or psychiatric illnesses that might be the cause of the fatigue and other symptoms, whereas the new SEID criteria<sup>1</sup> classify a number of formerly exclusionary conditions as comorbidities rather than exclusions. Regarding the SEID case definition, Komaroff<sup>3</sup> suggests that: "It will likely encompass a more homogeneous and sicker group of persons than the past case definitions." A key question is whether the new IOM case definition will accomplish these objectives.

## New criteria

To determine whether the new SEID case definition identifies a more impaired and homogenous group of patients, Jason, Sunnquist, and Brown et al.<sup>12</sup> analyzed archival samples from tertiary care settings, a BioBank, and other forums; each sample had applied a

different patient recruitment method. Participants included 796 patients from the United States, Great Britain, and Norway. We compared the SEID case definition to the previous Fukuda et al.<sup>4</sup> case definition for CFS, the International Consensus Criteria for myalgic encephalomyelitis (ME-ICC),<sup>10</sup> the Canadian myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) definition,<sup>9</sup> and a case definition developed through empirical methods (4-item empiric criteria).<sup>13</sup> Findings indicated that the SEID criteria identified 88% of participants in the samples analyzed, a similar group to the 92% that met the Fukuda criteria.<sup>12</sup> When the SEID case definition was compared to the 4-item empiric criteria, the findings indicated that the 4-item empiric criteria identified a smaller, more functionally impaired and symptomatic group of patients. This study suggested that the SEID criteria appear to identify a group comparable in size to that identified by the Fukuda et al. criteria, but larger in size to the group identified by the Canadian ME/CFS and ME-ICC criteria. Furthermore, the SEID criteria select more patients with less impairment and fewer symptoms than the 4-item empiric criteria.

In addition, this study<sup>12</sup> examined the percentage of participants who met each component of the SEID criteria. Only 67% of patients reported orthostatic impairment, a considerably lower percentage than what was found for other core symptoms. Moreover, the option of having orthostatic intolerance instead of cognitive impairment enabled just 2% more participants to meet SEID criteria than had the definition simply required cognitive impairment. Thus, the inclusion of orthostatic intolerance in the SEID criteria does not appear to significantly impact case definition fulfillment, so its inclusion in these criteria requires further justification.

This study<sup>12</sup> suggests that, among patients who are referred to specialty clinics or who self-identify as having CFS, the SEID criteria<sup>1</sup> select approximately the same group of participants who meet the older Fukuda et al.<sup>4</sup> CFS criteria. However, most individuals in these samples had already been diagnosed with ME or CFS by a physician, who likely accounted for exclusionary conditions when making a diagnosis; thus, few individuals with exclusionary illnesses were present in this study's sample. Community-based samples or samples that include individuals with other illnesses might contain many more participants with fatiguing medical or psychiatric conditions; thus, the SEID criteria<sup>1</sup> might identify a larger proportion of individuals in these types of samples as having the illness than would the Fukuda et al.<sup>4</sup> CFS criteria.

TABLE 1 provides the data that were included in Jason et al.,<sup>12</sup> as well as some additional comparisons, including an even more restrictive case definition of ME and several control groups. This table indicates what percentage of individuals from various samples meet each case definition, including the Fukuda et al.<sup>4</sup> criteria, the SEID criteria,<sup>1</sup> the Canadian Clinical ME/CFS criteria,<sup>9</sup> the 4-item empiric criteria,<sup>13</sup> the ME-ICC criteria,<sup>10</sup> and the ME criteria of Ramsay.<sup>14</sup> More descriptions of the samples (listed on rows in TABLE 1) and how they were recruited is provided elsewhere.<sup>12</sup> It is of interest that the ME case definition of Ramsay identified the fewest patients (20%), and this was primarily due to the criteria requiring a sudden onset of symptoms. While the Fukuda criteria identified the most patients (92%), this percentage was not much higher than the percentage who met the SEID criteria (88%). However, we now for the first time present data on the percent of controls who were

identified as having SEID in several samples. In the DePaul sample, 18% of undergraduates met the SEID criteria, whereas in the Bio-Bank sample, only 4% of controls met the SEID criteria. Comparable findings were also found for those diagnosed with the general Fukuda et al.<sup>4</sup> criteria, but not the other more restrictive criteria. BioBank control participants were required to be in good physical and mental health and could not have a substance use disorder or a disorder that causes immunosuppression; thus, fewer fulfilled SEID<sup>1</sup> or Fukuda et al.<sup>4</sup> criteria. However, the De-Paul control sample did not preclude students with health conditions from enrolling in the sample. As many college students likely experience various stressors or fatigue, a larger percentage of the DePaul control sample fulfilled the SEID<sup>1</sup> and Fukuda et al.<sup>4</sup> criteria.

We next will review the new SEID criteria's<sup>1</sup> position regarding exclusionary conditions. In the prior Fukuda et al.<sup>4</sup> criteria, there are many exclusionary illnesses that preclude diagnosis, as they might constitute the cause of an individual's symptoms. For the newly proposed SEID criteria, details about exclusions are provided within the IOM's Report Guide for Clinicians,<sup>15</sup> where it states: "The presence of other illnesses should not preclude patients from receiving a diagnosis of ME/CFS (SEID) except in the unlikely event that all symptoms can be accounted for by these other illnesses." The word "unlikely" conveys the impression that most other illnesses would be considered comorbid and not exclusionary as they probably would not account for the unique SEID symptoms. However, the core IOM symptoms are not unique to SEID, as other illnesses have comparable symptoms (eg, cancer, Hashimoto, lupus, chronic heart failure, multiple sclerosis, etc.). If treatment resolved all the SEID symptoms, then the patient would be classified as having another illness; however, if the treatment does not resolve the issues, then the condition is comorbid with SEID. In other words, the ability to determine if an illness is exclusionary rests on its successful treatment, and clearly, many chronic illnesses do not have treatments that cure or alleviate all symptoms. It is unclear whether the SEID case definition<sup>1</sup> could inappropriately include cases of purely affective disorders, such as major depressive disorder with melancholic features. Furthermore, SEID symptoms may also be experienced by individuals with other autoimmune illnesses such as MS and lupus. Using archival data, Jason et al.<sup>16</sup> recently evaluated whether the SEID case definition could accurately distinguish individuals with a physician diagnosis of CFS from individuals diagnosed with other illnesses. Data from 4 distinct studies were examined; each study had applied a different case ascertainment method, and samples were collected from tertiary care and community-based settings, as well as from patients who self-reported a diagnosis. Results indicated that a high percentage of individuals with other medical illnesses fulfilled the SEID criteria; therefore, many individuals with autoimmune and other health conditions who had previously been excluded from meeting case definitions will now be classified as having comorbid SEID (eg, 48% of those with a clear medical reason for their fatigue met the SEID criteria).<sup>16</sup>

Data from a community-based sample indicated that the SEID prevalence rate would be 2.8 times as great as the rate found when the Fukuda et al.<sup>4</sup> criteria were applied. In addition, the erroneous inclusion of individuals with primary psychiatric conditions in SEID samples would have detrimental consequences for the interpretation of epidemiological, etiological, and treatment efficacy findings for people with this illness. For example, 47% of a sample of individuals with melancholic depression met the SEID criteria.<sup>16</sup> Including individuals in

treatment studies who have a primary affective disorder but were misdiagnosed with SEID will lead to difficulties in interpreting treatment effects for individuals with ME. It is unfortunate that the report lacked a recommendation for a mental health evaluation or structured clinical interview, especially given that some SEID symptoms can overlap with symptoms of primary affective or mood disorders.

## Name change

Following the release of the IOM report,<sup>1</sup> David Tuller, a reporter for the *New York Times*, wrote a story about the new name and case definition.<sup>17</sup> This reporter interviewed the first author (Leonard Jason), who was quoted as saying: “The committee has come up with a name without vetting it. And they will basically get a tremendous amount of discontent and dissatisfaction right from the starting point, because the patients want something very different.” Following the publication of this newspaper story, the first author received many emails from patients from around the country, and some of the critical comments included: “This new name is an abomination!”; “Absolutely outrageous and intolerable!”; “I find it highly offensive and misleading.”; “It is pathetic, degrading and demeaning.”; and “It is the equivalent of calling Parkinson’s Disease: Systemic Shaking Intolerance Disease.”

A cognizance of the history of imposed name changes for this illness over the past 3 decades can contribute to the field’s understanding of these types of patient reactions. The term myalgic encephalomyelitis (ME) had initially been used to refer to this illness, but the Centers for Disease Control subsequently renamed the illness CFS.<sup>18</sup> Patients felt that the word “fatigue” trivialized their illness, as fatigue is generally regarded as a common symptom experienced by many otherwise healthy individuals. To provide a concrete example, if bronchitis or emphysema were called “chronic cough syndrome,” this name would similarly trivialize these conditions. In addition, patients believe that the name CFS has contributed to the negative attitudes expressed by health care providers and the general public toward individuals with the illness. Even though CFS is an illness as debilitating as type 2 diabetes mellitus, congestive heart failure, multiple sclerosis, and end-stage renal disease, 95% of individuals seeking medical treatment for CFS reported feelings of estrangement<sup>19</sup>; 85% of clinicians view CFS as a wholly or partially psychiatric disorder<sup>20</sup>; and hundreds of thousands of patients cannot find a single knowledgeable and sympathetic physician to care for them.<sup>21</sup> Patients have professed a need for a more medically-driven illness name, and our research group found that, when encountered with terms such as ME, research participants were more likely to attribute a physiological cause to the illness.<sup>22</sup>

Over the last decade, patient demands for change have grown louder.<sup>23</sup> New names have been given to several patient organizations (eg, the Patient Alliance for Neuro-endocrine-immune Disorders Organization for Research and Advocacy and the Myalgic Encephalomyelitis Society of America) and research and clinical settings (Whittemore/Peterson Institute for Neuro-Immune Disease). Even the federal government has begun to use the term ME/CFS, and the organization of researchers that study this illness changed their name to the International Association of CFS/ME. Many activist groups would like the original term, myalgic encephalomyelitis, to replace the name CFS, but other names have also been proposed, such as neuro-endocrine-immune dysfunction syndrome.<sup>24</sup> Effecting a

name change is a complicated endeavor, but developing a new name, such as SEID, without close contact with a number of key constituents will likely engender mixed reactions.

After a number of patient activists had contacted the first author to express thoughts on the IOM report,<sup>1</sup> the first author decided to write a blog post.<sup>25</sup> Its publication led to subsequent conversations with a number of patient activists who determined that it might be useful to gather patient opinions of the name change. Lisa Petrison, from the Paradigm Change organization, ultimately conducted a poll of 1147 people.<sup>26</sup> Approximately 62% of respondents rated the name SEID as “pretty bad” or “very bad.” In addition, the majority of respondents expressed negative opinions about the naming process and governmental use of the proposed name. With such disapproval among patient groups, it is less likely that this new name will gain the types of support required to actualize the adoption of the SEID term.

## Discussion

The IOM included panel members who are seasoned and experienced researchers and clinicians in the ME and CFS fields. Their contributions to this report are important in that they highlighted the seriousness of this illness and garnered considerable media attention for it. However, these positive developments might be dampened by patient reactions to the name change and the findings reported above that indicate the potential for the SEID criteria<sup>1</sup> to identify a more heterogeneous group than did the previous case definitions. The IOM did solicit opinions from many patients and scientists; even the first author of this article was invited to address the IOM committee regarding case definition issues. For IOM initiatives, it is understandable that critical decisions were kept secret until the full report is published. However, the effort to produce a fair and unbiased report reduced transparency in the process of developing the new name and diagnostic criteria for CFS. In an area where patients have been historically excluded and disempowered, a transparent, interactive, and open process becomes more important in making these types of critical decisions.

This article summarized several empirical approaches that were used to evaluate the SEID criteria.<sup>1</sup> While the IOM report<sup>1</sup> cited empirically-driven studies (eg, Jason et al.<sup>13</sup>) in the generation of its recommendations, further empirical work is required to fully evaluate these criteria. The first author has elsewhere suggested that solely empirical, rather than consensus, methods should be applied in the generation and evaluation of a case definition for this illness.<sup>27</sup>

The recent IOM report is being widely discussed among academics and the patient community.<sup>25,27,28</sup> There is also a need to consider how these recommendations could affect patients in other countries, given the prestige associated with the IOM report. Based on the findings and data reported in this article, we would recommend the implementation of participatory mechanisms for ongoing data collection and interactive feedback, ones that are vetted by broad-based gatekeepers, including scientists, patients, and government groups. Either the Chronic Fatigue Syndrome Advisory Committee (that makes recommendations to the Secretary of US Department of Health and Human Services) or the International Association of ME/CFS (the scientific organization) could appoint a name change working group and a case definition working group with international membership. This working

groups could engage in a process of polling patients and scientists, collecting and summarizing data, sharing the results with large constituencies, and maintaining a process that is collaborative, open, interactive, and inclusive. Key gatekeepers including the patients, scientists, clinicians, and government officials could work collaboratively and transparently to build a consensus for change, and most critically, to ensure that all parties are involved in the decision-making process.

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Analysis of case definition criteria in chronic fatigue syndrome (n = 795) patients and controls (n = 185)

**TABLE 1**

Sample	Case definition					
	Fukuda	SEID	Canadian	4-item empiric	ME-ICC	ME
DePaul						
CFS	96 (182)	91 (197)	77 (146)	60 (125)	57 (208)	28 (55)
control	17 (13)	18 (17)	3 (2)	8 (7)	1 (1)	0 (0)
BioBank						
CFS	93 (225)	88 (211)	73 (176)	61 (145)	NA <sup>a</sup>	NA <sup>a</sup>
control	4 (3)	4 (3)	1 (1)	1 (1)	NA <sup>a</sup>	NA <sup>a</sup>
Newcastle						
CFS	87 (83)	82 (82)	73 (70)	51 (51)	58 (58)	15 (14)
Norway						
CFS	90 (201)	88 (212)	77 (173)	67 (230)	62 (143)	14 (32)
total						
CFS	92 (691)	88 (702)	76 (565)	61 (475)	60 (320)	20 (117)
control	10 (16)	11 (20)	2 (3)	5 (8)	1 (1)	0 (0)

Data are presented as number (percentage) of patients.

<sup>a</sup>The percentage of participants cannot be computed for the ME and ME-ICC criteria in the BioBank sample as it was collected prior to a revision of the DePaul Symptom Questionnaire that included additional items necessary to assess the symptoms for these criteria.

Abbreviations: CFS, chronic fatigue syndrome; NA, not applicable