

# **Recommendations of the Name Change Workgroup Presented to DHHS CFS Advisory Committee**

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Workgroup members:

Carol Lavrich, K. Kimberly Kenney, Charles Lapp, John Herd, Daniel Kahn, Susan Levine,

Nancy G. Klimas, and Leonard A. Jason

## **I. Introduction**

The illness known as chronic fatigue syndrome (CFS), has over the years been referred to by a variety of names. Because the names for this illness are widely believed to be inadequate, the U.S. Department of Health and Human Services CFS Coordinating Committee established the Name Change Workgroup (NCW). Its charge was to investigate name change issues and present name change recommendations. The NCW reviewed the published CFS/ME literature, communicated with researchers, patients, and physicians, and conducted several surveys to further gauge opinions of various stakeholders (1,2). Based on these communications, the NCW has established that there are several different groups of stakeholders with strong feelings about changing the name. To assess all the data, the NCW has held regular discussions for three years and debated the relative merits of stakeholder concerns, a variety of potential names, and implementation issues. Based on these discussions, the NCW has concluded the following:

1. The vast majority of patients and physicians believe that the current name, CFS, too narrowly focuses upon a single, poorly defined symptom (fatigue) and profoundly promotes misunderstanding of the illness.
2. Patients feel the name CFS has substantially contributed to the disparaging manner in which they are perceived and treated by physicians, family, and the general public. They also believe that this misunderstanding has directly and negatively impacted the quality of medical care and support they are able to obtain. Research conducted by a DePaul University group led by Dr. Leonard Jason validates the adverse influence of name impact (3).
3. No one name is the obvious choice based on the current state of the science, nor can a single name fulfill all of the demands of all interested parties. We recommend that a new name serve as an umbrella term. Under that term, subgroups of patients can be more accurately stratified according to variations in illness presentation, pathophysiology, results of diagnostic testing, or other factors.
4. CFS is a serious and complex illness, that like several other significant and recognized conditions, is best categorized as a syndrome. A syndrome is a collection of signs and symptoms that when taken as a whole under the appropriate conditions, define the illness. Utilization of such an approach with the condition is analogous to the medical community's traditional approach to other serious organic syndromes such as diabetes, Lupus, Organic Brain Syndrome, and Multiple Sclerosis.

## **II. Factors Involved in our Recommendation**

Formulation of our recommendations was guided by several important principles. First, the name must not

imply that the etiology of the syndrome or its pathogenesis is clearly understood by the biomedical community. Second, it must reflect the common symptoms reported by most patients with the condition without overemphasizing any one system. Third, our recommendations must be supported by data published in the peer-reviewed literature.

The number of symptoms reported by patients with the syndrome is very large (4). However, most of the commonly reported symptoms are associated with or may be indicative of an aberration or dysfunction of the neurologic, neuroendocrine, and/or immunologic systems. The following selected scientific publications provide a sound basis for a new name that reflects common symptoms associated with these systems. The articles were selected because they have withstood scientific scrutiny and represent critical findings. While other publications are available, the chosen articles are widely respected, cited, and felt to be representative of the current understanding of the science. For purposes of this document, the articles have been categorized into their relevant subsections pertaining to each of the body systems.

## ***A. Neurologic System***

### Autonomic nervous system (including orthostatic intolerance)

Several authors have published findings demonstrating that some of the symptoms seen with this syndrome are associated with autonomic nervous system dysfunction, predominantly blood pressure control.

Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA* 1995; 274:961-967.

Schondorf R, Freeman R. The importance of orthostatic intolerance in the chronic fatigue syndrome. 1999 *Am J Med Sci* 1999;317(2):117-123.

Freeman R, Komaroff A. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med* 1997;102:357-364.

### Neuroendocrine System

The best studied evidence of neuroendocrine dysfunction involves the hypothalamic-pituitary-adrenal axis.

Demitrak MA, Dale JK, Straus SE, et al. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab* 1991;73:1223-1234.

Scott LV, Medbak S, Dinan TG. Blunted adrenocorticotropin and cortisol responses to corticotropin-releasing hormone stimulation in chronic fatigue syndrome. *Acta Psychiatr Scand* 1998;97:450-457.

### Neurocognitive Problems

Neurocognitive symptoms are reported with relatively high frequency in the syndrome. In addition to problems with memory and concentration, information processing functions appear to be abnormal. Many meritorious articles have been published, but at least one seems to be scientifically robust and has not been substantially challenged by other publications.

DeLuca J, Johnson SK, Ellis SP, Natelson BH. Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease. *J Neurol Neurosurg Psychiatry* 1997;62:151-155.

## ***B. The Immune System***

Several articles have been published investigating the relationship between the immunologic system and chronic fatigue syndrome. The best validated work and most consistent findings demonstrate decreased function of natural killer cells and reduced responses of T cells to mitogens and other specific antigens. The literature also supports evidence of chronic immune activation in CFS, with increasing emphasis on cytokine dysregulation.

Caligiuri M, Murry C, Buchwald D, et al. Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. *J Immunol* 1987;139:3306-3313.

Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbio* 1990;28:1403-1410.

Patarca R, Klimas N, Sandler D, Garcia MV, Fletcher MA. Interindividual immune status variation patterns in patients with chronic fatigue syndrome: association with gender and tumor necrosis factor system. *J of CFS* 2(1):7-41, 1996.

Cannon JG, Angel JB, Abad LW, Vannier E, Mileno MD, Fagioli L, Wolff SM, Komaroff AL. Interleukin-1 beta, interleukin-1 receptor antagonist, and soluble interleukin-1 receptor type II secretion in chronic fatigue syndrome. *Journal of Clin Imm* 17(3):253-61, 1997.

Sudanolnik RJ, Peterson DL, O'Brien K, Cheney PR et al. Biochemical evidence for a novel low molecular weight 2-5A-dependent Rnase L in chronic fatigue syndrome. *J of Interferon & Cytokine Res.* 17(7):377-85, 1997

### **III. Recommendations of the NCW**

The NCW recommends that we introduce a new term called neuroendocrineimmune dysfunction syndrome, or NDS, along with sub-group recommendations, to be described below. The recommendations are based on 1) the profile and frequency of the commonly reported symptoms of patients with chronic fatigue syndrome, and, 2) the published evidence supports an aberration or dysfunction of the neurologic, neuroendocrine, and immunologic systems. The term is in accordance with the principles outlined in Section II, above. Creating the term NDS does not imply that the etiology or pathophysiology is understood. The term is broad enough to encompass the most commonly reported symptoms. It is quite reasonable to conclude that the commonly reported symptoms are associated with or referable to the neurologic, neuroendocrine, and immunologic systems.

"Neuroendocrineimmune" is a long word but there are reasons for keeping it as one term. Neuroendocrine split off by itself puts undue emphasis on the neuroendocrine axis or system. Such an approach would be too focused, and some health care workers might then incorrectly assume that the illness is solely related to psychiatric conditions in which other neuroendocrine abnormalities have been documented.

The term dysfunction is warranted by the literature that indicates numerous body systems are not functioning properly. Therefore the word provides both meaning and legitimacy to the term. Dysfunction is a medical term and it does not connote psychiatric origin as there are many metabolic/physiological dysfunctions that have biological underpinnings.

The word syndrome emphasizes the fact that this illness is a collection of signs and symptoms that in their totality define this illness. By appropriately using the word syndrome, there is a better prospect of having the term accepted by the medical community.

The formal charge of the Name Change Working Group does not extend to developing diagnostic criteria for NDS or creating a new case definition. Parallel, but independent efforts are occurring by a group assembled by the Centers for Disease Control & Prevention to revise the Fukuda et al. (1994) research case definition. There is also a group led by Canadian health officials and advocates to develop diagnostic criteria for a Canadian clinical case definition. There are members of the Name Change Working Group involved in both of these other efforts.

Despite these efforts, it will likely be many years before diagnostic criteria are developed, validated and widely accepted. We believe that our recommendations should be adopted and implemented now.

#### **IV. Utilization of NDS**

Advances in biomedical research should ultimately discover the pathophysiology or cause(s) of NDS. Until the etiology is known, the descriptive term NDS should be used for the reasons outlined above. The NCW anticipates that the biomedical community will find that subgroups or subtypes of NDS provide useful nosology. Thus, the use of subgroup stratification offers flexibility and adaptability to the inevitable advances based on scientific research. This approach also promotes more accurate understanding of the illness when compared to the current name, chronic fatigue syndrome.

In the past there have been many efforts to categorize CFS based on a variety of criteria. Some of the more prominent of these subgroups have been used by scientists and patients. They are included and reviewed below. The NCW recommendation includes these subgroups in an effort to provide a conceptual framework for the term NDS, and to better define the status of other names in use vis-à-vis our recommendations. The term Neuroendocrineimmune Dysfunction Syndrome (NDS) is being recommended as an umbrella term, representing a broader condition than CFS.

Unfortunately, uncontrolled patient heterogeneity in empirical studies is a consequence of ignoring the issue of sub-classification (5,6). When unique patient groups are combined, any distinctions pertaining to specific subtypes of CFS become blurred. There has been a lack of consistency in such laboratory findings, which may be a function of combining distinctive groups of patients into a large heterogeneous group rather than analyzing them within subtypes. Researchers have begun to determine the validity of an approach that involves subdividing their patients into groups. This proposal will lead investigators to make efforts in future studies to sub-group samples (e.g., NDS-Orthostatic Intolerance), and thus might help identify more consistent pathophysiological markers and therapeutic interventions for this illness. At such time, we believe that our proposed umbrella term (NDS) will accommodate and be compatible with research-driven subtyping.

#### **V. Utilization of subgroups**

Under the Neuroendocrineimmune dysfunction syndrome, we recommend the following subtypes:

- A. Myalgic Encephalomyelitis
- B. Fukuda et al. (1994) criteria
- C. Canadian clinical criteria
- D. Gulf War Syndrome

*Myalgic Encephalomyelitis (ME):* Myalgic Encephalomyelitis (ME) has been documented in the medical literature since 1934 in both epidemic and sporadic forms [7]. ME is a systemic illness. Patients experience generalized or localized muscle weakness following minimal exertion with prolonged recovery time. Additionally the illness encompasses Central Nervous System involvement (e.g., sleep disorders,

autonomic dysfunction, cognitive dysfunction disturbances, endocrine dysfunction, proprioceptive dysfunction, sensory dysfunction) and variable involvement of cardiac and other bodily systems. ME has marked fluctuation of symptoms over time and an extended relapsing course with a tendency to chronicity. The extreme post-exertional muscle fatiguability (and increased symptomatology upon exertion) in patients with ME is quite distinct from chronic tiredness. ME has been formally classified by the World Health Organization as a neurological disorder in the International Classification of Diseases (ICD) since 1969 and remains classified in the current ICD as a neurological disorder (ICD 10. G.93.3). Some patient groups have endorsed the term Myalgic Encephalopathy, because the term encephalopathy does not necessarily require an inflammation in the central nervous system. A diagnosis of ME requires central nervous system dysfunction and exercise intolerance. In the Fukuda et al. (1994) criteria below, these symptoms are included in the list of eight characteristic symptoms, of which four must be present; therefore, it is possible for patients to not have these characteristic features of ME using the Fukuda et al. criteria (8,9). The NCW received a petition with over 5,000 signatures calling for recognition of ME.

*Fukuda criteria:* The Holmes et al. (1988) case definition was first introduced in 1988, and it was revised in the Fukuda et al. (1994) case definition. The Fukuda et al. (1994) case definition is being used by researchers internationally. It is in the process of being examined and revised by an international working group. The differential criteria for the Fukuda et al. (1994) case definition require at least four of the following symptoms: sore throat, lymph node pain, muscle pain, joint pain, postexertional malaise, headaches of a new or different type, memory and concentration difficulties, and unrefreshing sleep. However, some patients have been labeled as having CFS with this criteria, but have not had the classic symptoms associated with the syndrome, including postexertional malaise and/or memory and concentration difficulties. This has led to the selection of a heterogeneous population. In addition, by having a requirement of at least four of the symptoms and by having many medical and psychiatric exclusionary illnesses, the Fukuda et al. case definition can also be too restrictive so that some patients who in all likelihood have the syndrome fail to meet this definition. Scientists may continue to use the NDS-Fukuda case definition in order to compare patients across different settings. The name CFS will no longer be used given the stigma associated with this term. We fully expect that the NDS-Fukuda case definition will be compared to other criteria and subtypes in future research. Also, by retaining this population as a subtype it would be possible to differentiate it from other subtypes.

*Canadian Clinical Criteria:* A consensus panel in Canada has recently proposed a clinical case definition. The proposed criteria differ from the Fukuda research criteria. The Canadian Clinical definition specifies that the illness persist for at least six months. In addition, there must be a marked degree of new onset of unexplained, persistent or recurrent physical or mental fatigue that substantially reduces activity level. Post-exertional malaise occurs with loss of physical or mental stamina, rapid muscle or cognitive fatigability, usually with twenty-four hours or longer to recover. There should be unrefreshing sleep, or sleep quantity or rhythm disturbance, and a significant degree of arthralgia and/or myalgia. There are a small number of patients with no pain or sleep dysfunction. A diagnosis can only be given when these individuals have a classical case with an infectious illness onset. In addition, there need to be two or more neurocognitive manifestations (e.g., confusion, impairment of concentration and short term-memory). Finally, there must be at least one symptom from two of the following categories: autonomic manifestations (neurally mediated hypotension, light headedness), neuroendocrine manifestations (e.g., recurrent feelings of feverishness and cold extremities), and immune manifestations (e.g., recurrent sore throats). These criteria were developed specifically to be used in clinical practice (10).

*Gulf War Syndrome:* GWS is characterized by symptoms that appear to reflect a spectrum of neurologic injury involving the central, peripheral, and autonomic nervous systems (11). The symptomatology includes problems with attention, memory, thinking, and reasoning, as well as insomnia, depression, daytime sleepiness, headaches, disorientation, balance disturbances, vertigo, sexual dysfunction, muscle

and joint pains, muscle fatigue, difficulty lifting, and extremity paresthesias (numbness). Five years after the Persian Gulf War, clusters of these symptoms continued to be reported by an estimated 5,000 to 80,000 of the U.S. veterans involved in the 1991 Gulf war against Iraq (11).

## VI. Conclusion

We feel that these recommendations will provide a broader umbrella than do other purposefully restrictive criteria like those of the current Fukuda criteria. In the past, individuals who had disabling chronic fatigue for 6 or more months were designated as having ICF (Idiopathic Chronic Fatigue) or CFS. We believe that evidence-based research must drive the development of these sub-groups. We do not believe that this proposal will open the door to unfair psychological interpretation of this condition any more than it will encourage any other distorted interpretations of the illness. Rather, we believe that the subtypes or sub-categories will aid appreciably in identifying biomarkers of the syndrome and provide a practical working construct for clinicians and biomedical researchers from a wide variety of disciplines. We do recognize that there are risks of a name change as some people feel that a name change at this time is imprudent. However, after working as a group and collecting data from multiple stakeholders for three years, our recommendation is to make the changes mentioned in this document as soon as possible.

At the January 2000 meeting of the DHHS CFS Coordinating Committee (CFSCC), a motion was approved to hold a special name change session in conjunction with the next meeting of the CFSCC (or its successor advisory committee). The accepted motion was to address the impact of our recommendations on issues related to medical reimbursement, disability benefits, managed care, etc., as well as the adaptation consideration for the various agencies. Although the CFSCC has been dormant since that time, it is imperative that experts in these fields be involved in developing an implementation plan for our recommendations. Such planning will be imperative to ensure that a change does not impede patients' access to health care systems, medical insurance reimbursement, disability benefits and other federal and state assistance programs.

It is crucial to involve medical educators and thought-leaders from the medical community in developing an implementation plan for promotion and adoption of the recommendations if they are to become broadly utilized.

If approved by the Secretary for Health, the recommendations will need to be used in federally sponsored publications and education efforts. Widespread acceptance and adoption of this new paradigm will only be accomplished through a broad, multi-year education campaign.

The NCW urges the CFS Advisory Committee to support adoption of the term NDS, in conjunction with subgroup stratification as described. We believe that it meets the current need for more accurate and specific diagnostic labels while allowing room for the recognition of additional sub-grouping as biomedical advances take place.

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