

Pathways to Prevention: Advancing the research on ME/CFS

Public Comment on the P2P Draft Report

by Lars Lagerstrand, MD, PhD, Associate Professor of Clinical Physiology

I would like to submit the following comment on the Draft Report about ME/CFS, referring to the 403 line version:

To a large extent I find the report very pertinent. The following are examples of sections I especially endorse and support:

Lines 7-8

Lines 63-64

Lines 68-70

Lines 82-26

"Specifically, it is critical to include patients with limited access to clinical services (e.g., non-ambulatory patients", lines 104-105

Lines 142-159

Lines 184-187

Lines 213-276

Lines 303-305

Line 390

I request that these sections stay within the final document.

One important area for improvement is to have the Final Report clearly state that the hallmark symptom of ME/CFS is actually not fatigue, but post-exertional malaise (PEM). As is stated in the Primer published by the professional organization IACFS/ME (International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis): *"The key feature of the syndrome, post-exertional malaise, is the exacerbation of symptoms following minimal physical or mental activity, which can persist for hours, days or even weeks."* (See Chronic Fatigue Syndrome/Myalgic Encephalomyelitis – Primer for Clinical Practitioners, 2014 Edition: <http://www.iacfsme.org/LinkClick.aspx?fileticket=Pi0KeD1c2M%3d&tabid=509>)

The fact that PEM, not fatigue (which is also found in many other illnesses), is the cardinal symptom of ME/CFS is also clear in the Canadian Consensus Criteria (CCC, Carruthers et al, 2003), where PEM is a mandatory symptom:

Item 2: Post-Exertional Malaise: *"There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period - usually 24 hours or longer."*

The CCC has become the preferred definition for most of the international experts in the field (both clinicians and researchers), not least due to this very fact; that it requires PEM for a diagnosis of ME/CFS to be made. Research (Jason et al, Marshall-Gradisnik et al) has shown that the CCC and other definitions where PEM is mandatory capture a smaller, more severely ill, more disabled and more homogenous patient group. Recognizing PEM as the distinguishing symptom is key to improving both the research field and clinical care for ME/CFS patients.

This position of the leading experts is echoed by clinicians with experience in ME/CFS as well as patients. Typical for ME/CFS is not fatigue (which is also found in many other illnesses), but PEM, the inability to manage even minor activity and the “crash” following activity where all symptoms flare up.

It is vital for the field that Post-Exertional Malaise be recognized as the cardinal symptom of ME/CFS. It is also of utmost importance that future research is based on criteria where PEM is a required symptom.

This needs to be incorporated in several sections of the Draft Report, for example

Line 2

Lines 58-59

Line 95-97

Lines 141-177

Conclusions (lines 368-403)

Furthermore, it would be valuable if the report mentioned some of the evidence of the physiological dysfunctions which are believed to play a role in PEM, such as:

Several groups have found abnormal results underpinning PEM in ME/CFS patients using clinical exercise testing. Using two cardiopulmonary exercise stress tests (CPET), spaced 24 hours apart (referred to as the Stevens Protocol), researchers have shown very distinct differences between ME/CFS patients’ performance on Day 2 compared to Day 1. There is an extensive literature on two-day CPET testing in many other patient groups, as well as healthy controls, and the normal pattern both among patients with other diseases and controls is to improve their measurements on Day 2.

By contrast, ME/CFS patients do significantly worse on Day 2. Several measures of energy production in ME/CFS patients decline in the second exercise test, suggesting damage occurring as a result of the first exercise period inhibits energy production afterwards – a highly unusual finding likely to be distinguishing for ME/CFS. These studies suggest that metabolic dysfunction is common in ME/CFS but that variations may occur. Further study is urgently needed to validate these findings and stratify subgroups.

See the studies listed below:

[J Transl Med. 2014. Inability of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients to Reproduce VO2peak Indicates Functional Impairment](#)

[Physical Therapy 2013. Discriminative Validity of Metabolic and Workload Measurements to Identify Individuals With Chronic Fatigue Syndrome](#)

[J Transl Med 2010: Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity.](#)

[Journal of Chronic Fatigue Syndrome 2007: Diminished Cardiopulmonary Capacity During Post-Exertional Malaise](#)

[J Women's Health 2010: Postexertional malaise in women with chronic fatigue syndrome](#)

Other researchers have found differing gene expression alterations following exercise in ME/CFS patients, see:

[Journal of Internal Medicine 2012: Gene expression alterations at baseline and following moderate exercise in patients with chronic fatigue syndrome and fibromyalgia syndrome.](#)

[Differences in metabolite-detecting, adrenergic, and immune gene expression after moderate exercise in patients with Chronic Fatigue Syndrome, patients with Multiple Sclerosis, and healthy controls](#)

It is vital that the sections "2. Create new knowledge" (lines 213-284) and "3. Improve methods and measures" (lines 285-309) in the Final Report include recommendations of further research into the physiological underpinnings of PEM, such as the fields of research mentioned above.

I would also briefly like to mention that Major Depressive Disorder is generally not seen as an overlapping condition. ME/CFS and MDD differ significantly in presentation. In the majority of cases ME/CFS is triggered by an infection, has immunological symptoms, is characterized by PEM, meaning exercise causes deterioration, and does not cause low self-esteem, self-reproach or low motivation. In MDD patients, by contrast, self-reproach and motivational issues are key features and MDD patients get better with exercise. It is fairly easy for a knowledgeable physician to distinguish between these two disorders. When a Depressive Disorder is found in a patient with ME/CFS it is usually secondary to the severe situation living with ME/CFS.

I therefore request that the statements in line 33 and line 94 about MDD being an

overlapping disorder are changed in the Final Report.

And, finally, I would like to echo what patient advocate Robert Miller said during the Workshop: that negligent levels of research funding have prevented medicine from solving ME/CFS and that the need above all others is for this be remedied. I request that the Final Report include a recommendation (for example near lines 212-220) that NIH shall set aside funds for ME/CFS research and raise the level of funding substantially. This recommendation should include set numbers and timelines, in order to ensure effective action.

Thank you for your consideration,

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