

Understanding Post-Exertional Malaise (PEM) a hallmark symptom of ME/CFS

Transcript of a video from 'Dialogues for a Neglected Illness'

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Dr Nigel Speight: Post-exertional malaise is the cardinal symptom of ME which distinguishes it from many other fatiguing illnesses like depression and cancer chemotherapy and things like that. A person who's depressed, who exerts themselves – exercise is actually quite good treatment for depression. But the post-exertional malaise that ME patients suffer is absolutely classical and for me is the clinching element in the diagnosis. It's also part of the, all current main orthodox definitions of the condition.

Dr Christopher Snell: Post-exertional malaise is a primary symptom of ME/CFS. It consists of decreased function and an exacerbation of symptoms usually following a physical event but it can also follow a cognitive or mental event and even an emotional event. Recovery time is highly variable, there can also be some delay in when it first appears, even two days after the triggering event.

Dr Nina Muirhead: I can cope with around 10 hours a week of umm increased activity or concentrating and I mainly do that at work. But if I take on any more, or there is something unpredicted about my week, then I can really suffer afterwards. To begin with that can often start with headaches or a sore throat coming on, feeling like I'm getting flulike or coming down with something, and then a couple of days later it really hits me and I literally can't get out of bed, and I feel as though I'm concussed, I can't concentrate and my level of functioning has to be taken down a couple of notches, until I get to a point where I can be stable again

Grace, ME/CFS patient: If I do more than I should, then sometimes it can make me feel ill straight away, and other times I can feel fine, for maybe a day or two afterwards and then it hits me and that's a particularly difficult thing to anticipate.

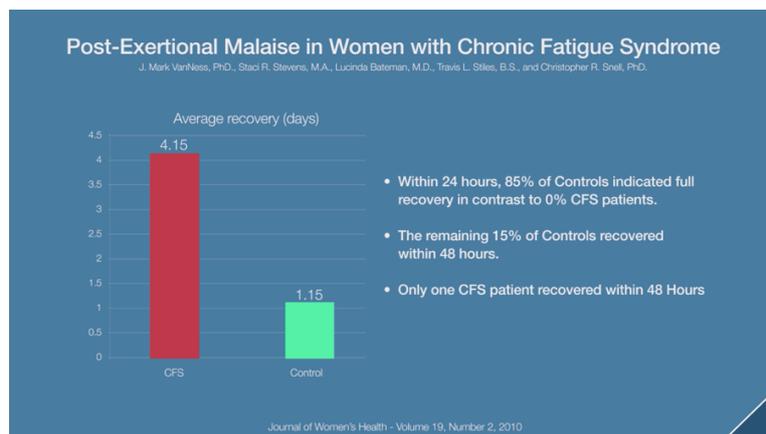
There's two ways for me. One is to do much too much in a short period of time, the alternative is doing slightly too much for a longer period of time. So for a week I might feel like I'm actually getting better and just stretch myself a little too far, and then I'll maybe have to take a few weeks to recover from that.

Dr Nigel Speight: It's important to realise that at the severe end of the spectrum, what we would regard as exertion.. they don't need to exert themselves properly for this phenomenon to operate and that simply reading a book or listening to a visitor or some sort of brain activity can be a form of exertion that leads to worsening.

In the USA, researchers at Harvard Medical School, the Workwell Foundation, the NIH and other centres, use objective measures to study the pathophysiology underlying exercise intolerance and post exertional malaise in ME/CFS

Staci Stevens: Post-exertional malaise is distinctly different in ME than in patients with heart disease, or lung disease or HIV. So we'll test our heart failure patients and they'll say that they are fatigued for a couple of days. We'll test a healthy individual and they may have some delayed onset muscle soreness, but it resolves. For ME patients, we test them, and there's a whole laundry list of symptoms that are atypical and abnormal. They have flu like symptoms, they have cognitive problems, they can't sleep, they get sick. And that's completely different than what we see in other conditions.

Dr Chris Snell: We provide an exercise stressor and we look at the effects of that on the individual. And one of the things that we see in post exertional malaise is a reduced function following even quite a low level physical activity.



You'll see excessive fatigue, you'll see a failure to recover, and we also see an inability to engage in physical activity for a period afterwards.

Prof Todd Davenport: We looked into a symptom cluster we identified based on an open report questionnaire after a test re-test protocol... 19 separate symptoms that we had classified, and those symptoms, fatigue, sleep abnormalities, cognitive abnormalities, immune abnormalities, shook out as being most significantly predictive. And in fact that symptom cluster had a positive predictive value of 92 % and a negative predictive value of about 81%. So this is the kind of thing that just by listening to your patient, can actually be the million dollar work up.

Invasive cardiopulmonary testing, used to detect early heart disease and pulmonary vascular disease, is revealing a ubiquitous pattern in ME/CFS -

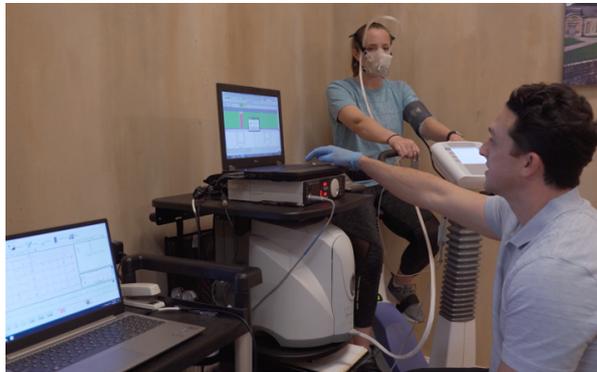
- low filling pressures / preload failure on the venous side of the heart: there appears to be impaired veno-constriction during upright exercise
- significant abnormalities of blood flow and systemic oxygen extraction, on the arterial side.

Dr David System: A number of changes happen with acute exercise - biochemical, neuro, humeral, neurogenic changes, that can happen as a result of exercise in an abnormal host on day one, that could have relevance to symptoms on day two. We think that there may be some evidence of inflammation and autoimmunity that may be provoked by the acute exercise on day one that lead to symptoms on for instance day two. I'm aware of some emerging data from the National Institutes of Health in the United States, using tests of mitochondrial function in peripheral blood mononuclear cells, that suggests that there is a humeral factor, in the plasma of ME patients, that elicits mitochondrial dysfunction in while cells, when the two are put together.

There are central nervous system changes and in particular inflammation, that have been shown by some of our collaborators in Boston. Working with functional MRI of the brain, they've been able to demonstrate that there's evidence of leptomeningeal and CNS, central nervous system inflammation, that is increased in the setting of post exertional malaise.

Dr Chris Snell: We use a technique called cardio pulmonary exercise testing.. Er it's well established, particularly in the field of heart disease. Essentially what we're measuring is how much oxygen are they using to provide energy to active muscles... It's one of the best measures of function, so it's accepted by a number of medical organisations and disability evaluation organisations including the American Social Security Administration, as a measure of what we call functional capacity. It's highly accurate, it's objective, which in the field of ME/CFS is quite rare to have objective measures of function. So we're able to equate somebody's oxygen consumption to their capacity to be physically active.

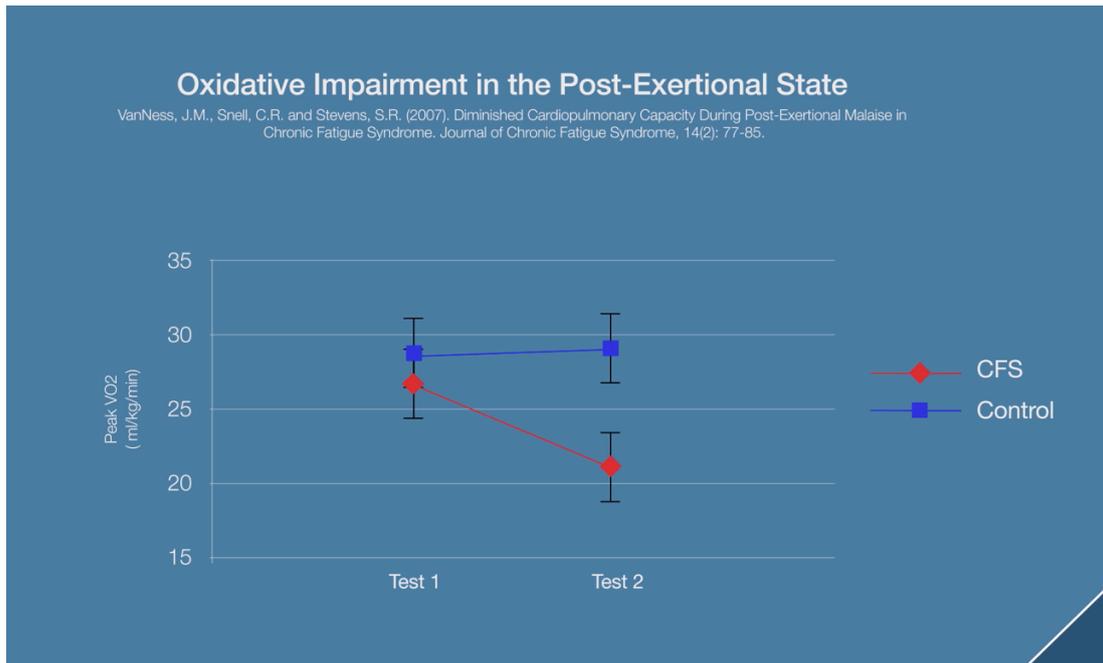
One of the things that we pioneered was the 2 day exercise test, where we give somebody an exercise test on day one, then we have them come back on day 2 and repeat that exercise test.



What we found was that many of our patients could not repeat their performance on day two, so there was a performance decrement between the two test. This is highly unusual and has not been documented in other illnesses. So even very sick people with cardiovascular disease, multiple sclerosis are able to repeat their exercise test performance on day 2, no matter how low it is.

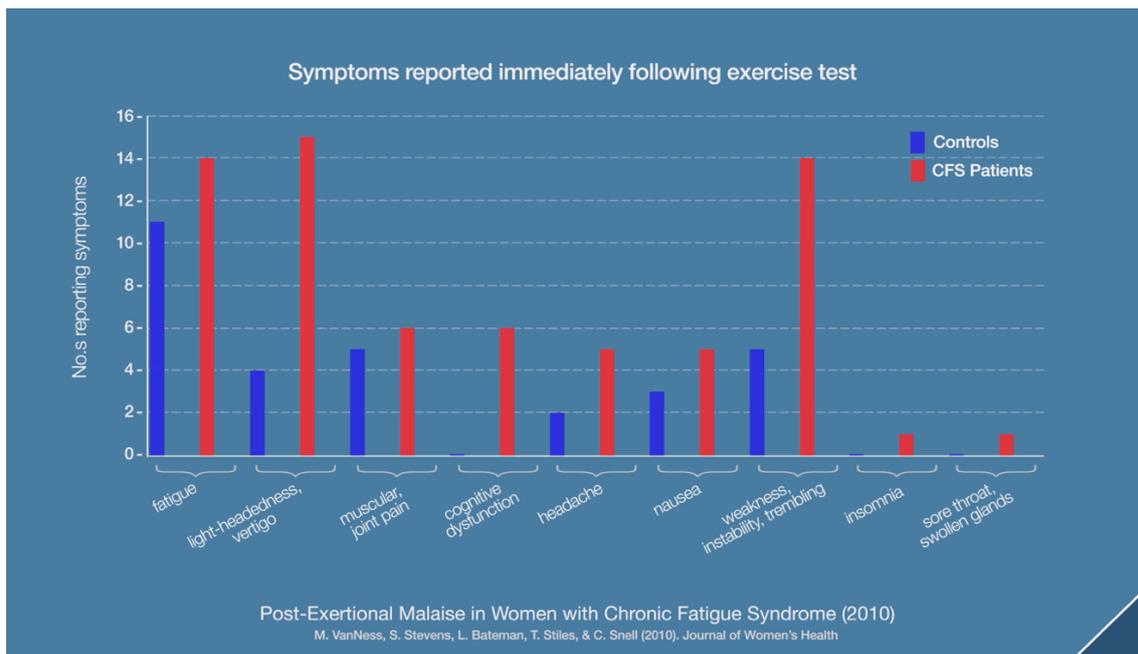
Prof Mark VanNess: We oftentimes refer to reliability of cardio pulmonary variables, and there's a number of very significant illnesses, like heart disease, cystic fibrosis, if they were to do an exercise test one day to the

next, you would not expect and you would not see any differences in those variables, because those illnesses don't have PEM. And when you compare those results, whether for control subject, subjects that's heavily deconditioned, or even a subject with a very significant illness, the results of the exercise test are very reliable, very reproducible.... and the same cannot be said for ME/CFS.

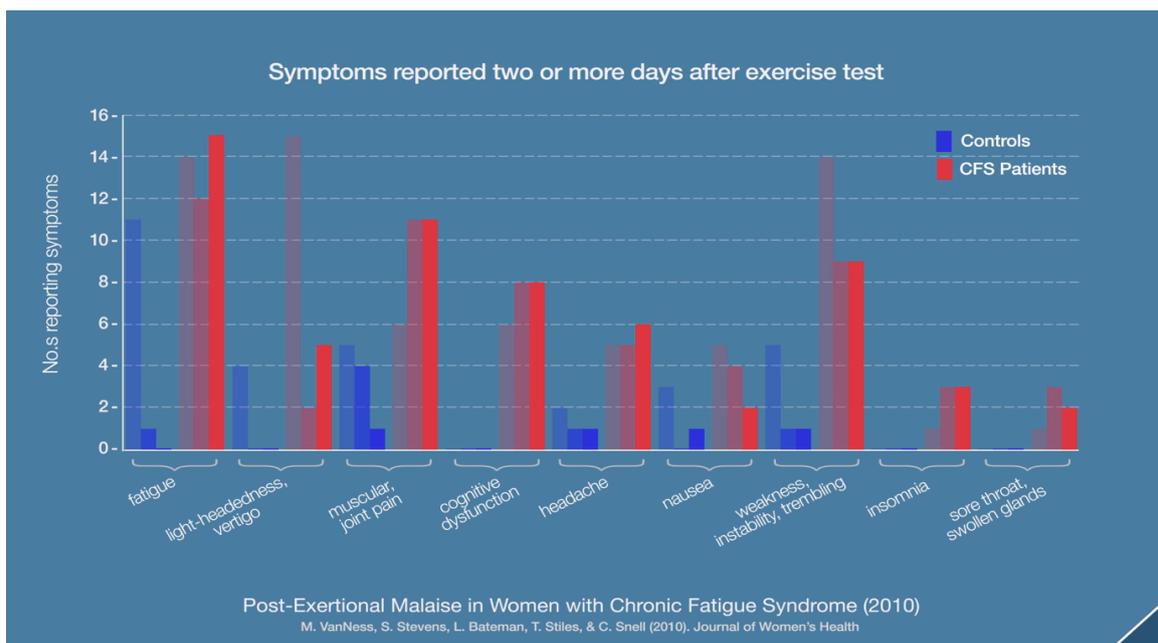


Those values typically decline from one day to the next, almost always a decline in measures such as heart rate at the anaerobic threshold, work output that the subject is capable of doing from one day to the next, and they're very objective comparisons because we're measuring the metabolic response to exercise and it provides a very realistic view of what is post-exertional malaise, especially when comparing to other illnesses.

Staci Stevens: Post-exertional malaise has immediate, short term and long term symptomology, that pairs with the pathophysiology. We do a cardio pulmonary exercise test that results in immediate symptoms and this is true whether you are a patient with ME or an elite athlete. Everybody has to stop on the bicycle because of symptoms, and those symptoms include things like, fatigue, pain, shortness of breath, dizziness, nausea. Those are immediate very normal responses to exceeding the anaerobic threshold.



The difference for the ME patient is that they experience those symptoms and then those symptoms begin to magnify. For a healthy individual, they experience those symptoms, they stop the test and then the symptoms begin to dissipate and completely disappear. ..and that can happen in a matter as quickly as 10 mins. However for your ME patients, they not only experience immediate symptoms, and those symptoms begin to magnify, they can then last for days.



Staci Stevens: Our short term model of PEM is that which lasts 2-4 days. It reflects exceeding the anaerobic threshold for extended periods or multiple times in a day. With the CPET we're ensuring that our patients are spending a good amount of time in anaerobic metabolism on both days. The consequences of that are symptoms like muscle and joint pain, cognitive dysfunction, headaches, sleep disturbance and we think that that reflects, not only the consequence of anaerobic metabolism, but then it begins to build and now we're seeing dysfunction in the areas of dysautonomia, as well as the Hypo-thalmo-pituitary Adrenal axis

The third area of PEM lasts 7 days or longer. And some patients report that it last weeks. It can even last months. The symptoms in this area are flu like symptoms, weakness, cardio pulmonary symptoms, and an overall decrease in function. Now we also have a sustained immune response.

In our more severely impaired patients, this is where we think they're living.

Symptoms following exercise - clarified by Workwell research.

- Immediate symptoms experienced by everyone! In **non-ME/CFS** people these dissipate quickly – fatigue, pain, shortness of breath, dizziness, nausea.
- Short term PEM – symptoms start to get worse and can last for 2-4 days - eg muscle and joint pain, cognitive dysfunction, headaches, sleep disturbance, sore throat
- Long term PEM – a week to months – a sustained immune response – flu-like symptoms, weakness, cardiopulmonary symptoms, and an overall decrease in function. Severely ill patients may be living in this state for years.

Prof Mark VanNess: Most of the ME/CFS patients that we see in our clinic, they typically report recovering within a few days – 3 to 4 days. Although that's a long and impaired recovery response, it's fairly typical of what many ME/CFS patients experience and we attribute that to the abnormal immune activation that is inhibiting the energy generation pathways. We do have a subgroup of patients that take many days to recover, sometimes even weeks to recover from a single bout of exercise.

Dr Chris Snell: Some people are confined to bed for up to three of four days following what is really quite a low level physical event. So one of the things we see with disability is that people are unable to work, because they'll go into work one day, they will do a full days work, they will bring on symptoms of post-exertional malaise because of the exertion that they're involved in throughout the work day and they are unable to go to work the next day. They're sick and they do not recover.

If a patient can avoid bringing on symptoms of PEM we've found that they are able to function in their daily lives much more efficiently. So you're avoiding the sickness. The key to that is something called **pacing** That means.., that's adjusting your energy output, your energy expenditure to a level below that level that is going to trigger symptoms of post-exertional malaise. We've found that the most likely trigger is a point called the anaerobic threshold. That happens at a very low level in ME/CFS. and if you exceed that level for any extended period of time, the likelihood is that you're going to elicit symptoms of post-exertional malaise. So with **pacing** what we try to do is we try to avoid that triggering event.

Staci Stevens: Post exertional malaise is central to understanding this illness and it's helpful for patients to understand it, it's helpful for providers to understand it and it's helpful for researchers to understand it. Without a foundation of this hallmark symptom we won't advance research, and providers will not be equipped to best treat their patients.

Post-Exertional Malaise (PEM) is an abnormal response to exertion. It involves both an exacerbation of symptoms and a loss of stamina and/or reduction in functional capacity.

It can be caused by any activities beyond those normally tolerated, whether a single event or a period of slightly 'overdoing'. These could involve –

- Physical stressors such as exercise, activities of daily living, orthostatic stress.
- Cognitive or mental activities and social interactions.
- Environmental and sensory stressors such as: Light, sounds, movement, temperature extremes, chemicals
- Emotional stress

PEM can be immediate but is typically delayed by a day or two and recovery time is abnormally prolonged, whether days, weeks, months or much longer. Overexertion can cause lasting relapse, with patients never returning to their preceding level of activity.

Contributors

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