

CFS and Exercise Intolerance

One of the key symptoms of Chronic Fatigue Syndrome and Myalgic Encephalomyelitis is exercise intolerance. (Others include cognitive dysfunction, sleep disturbances, pain and general fatigue.) Patients experience what has been called “post-exertional malaise” or “post-exertional neuroimmune exhaustion,” with worsening of their condition for days or weeks following even brief mild activity.

Dozens of studies have looked at this abnormal response to exercise, uncovering numerous physiological abnormalities. For instance, CFS patients experience abnormally increased inflammation, oxidative stress, C4a complement levels and intramuscular acidosis after exercise. For them, exercise also results in abnormal gene and heat shock protein expression, decreased cerebral oxygenation, lowered mitochondrial ATP, and extended abnormal pH.

Most people get a variety of positive effects from exercise, including increased energy, better sleep and decreased sensitivity to pain. CFS patients get the opposite: increased fatigue, insomnia, higher levels of pain and other negative symptoms.

Commonly CFS patients try to be active at a higher level than their bodies can tolerate. This generally leads to a “push-crash” pattern: a burst of activity is followed by an extended period of relapse and recovery. Thus, a challenge for CFS patients is how to remain even a little active without experiencing repeated “crashes.”

A team of psychiatrists from the UK has looked at the topic of exercise intolerance in a series of studies, the most recent of which was funded with \$8 million in UK government grants and published in March 2011 in the British medical journal *The Lancet*.

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M; PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 2011 Mar 5;377(9768):823-36. PMID: 21334061

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(11\)60096-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext)



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www.pacetrials.org/trialinfo.html

Building on previous work, the authors studied people with CFS and other fatiguing illnesses, using two techniques designed to help patients be a little active without suffering relapses.

One of the techniques, Graded Exercise Therapy (GET), is based on the observation that crashes in CFS patients generally occur when their heart rates become abnormally high. Thus, patients were taught to use a heart rate monitor when engaging in physical activity and exercise, and instructed to make sure that they did not exceed specific heart rate levels.

A second technique, Cognitive Behavioral Therapy (CBT), had patients carefully evaluate their desired activities and then set daily goals so that they would remain at modest levels of exercise and activity each day. The counselors also helped patients to consider how they could reduce potential sources of stress in their lives.

Patients using these techniques did an average of 10-15% better after 52 weeks than the controls in terms of their self-reported fatigue, their self-reported physical functioning and (for the GET condition only) the distance they could walk in six minutes. However, they did not come anywhere close to returning to normal levels on any measure. For instance, patients receiving GET were able to walk 379 meters in six minutes, compared to 348 meters for patients receiving no treatment and 631 meters for healthy people aged 65+ in another study (Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270-274, PMID: 10515400). They also experienced no cognitive improvements at all.

Another limitation of the study was that it did not include any CFS patients who were severely ill enough not to be able to attend the 14 or more therapy sessions required. Whether these techniques would be of any help to bedridden or housebound patients is unknown.

Many CFS patients have expressed unhappiness with this particular study and this line of research, for several reasons.

First, the research group generating the work has often seemed to be implying that the interventions were more effective in helping CFS patients than was actually the case. None of their techniques came anywhere close to returning subjects to normal lives, at



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most allowing them to become a little bit (10-15%) more physically functional with no cognitive improvements.

In addition, patients report that important people in their lives (such as caregivers, employers, teachers, family, friends and medical professionals) often do not have an accurate understanding of what the study entailed. They say that this has resulted in the general insistence that CFS patients could succeed in getting well if they would just exercise more or try harder -- even though these conclusions had nothing to do with the study.

Severely ill CFS patients point out that since bedridden and housebound individuals were not included in the study, the results should not be taken to apply to them.

UK patients report especially disturbing experiences with misapplied results of this line of research, with some patients getting permanently worse as a result of being held in mental hospitals and being forced to exercise. They object to the fact that GET and CBT now are the only treatments for CFS recognized by the UK government, and that practitioners who treat it with physical interventions (for instance, with vitamins) have been threatened with having their licenses taken away.

Following is a compilation of comments on the topic of CFS and exercise intolerance from a variety of physicians and researchers specializing in the disease; a detailed critique of the many methodological flaws of the PACE study; a review of the relevant medical literature; and a couple of media articles on the topic.

-Lisa Petrison, Ph.D.

CFS AND EXERCISE INTOLERANCE

DOCTOR AND RESEARCHER COMMENTS

Except where indicated, quotations were supplied by the named individuals specifically for this document.

Research shows that these disorders respond somewhat to cognitive behavioral therapy and exercise. "Somewhat" means you can improve symptoms a little with better coping and improved physical conditioning. We work on that every visit. It doesn't mean you have cured the disease. There are many patients with CFS who are severely intolerant of physical activity, and suffer greatly from attempts to exercise.

There are many factors that determine how well a person can improve from their symptoms. Some of it relates to motivation and discipline, but much of it relates to fate, the disease state, how long they've had it and how severe it is. I frequently encounter the stereotyping that patients who don't get better just aren't trying hard enough and that smart motivated ones do, but I don't believe it is that simple. It isn't consistent with my clinical experience.

Lucinda Bateman, M.D.
Salt Lake City, UT

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The most important consideration is finding a person who understands CFS. They need to be willing to listen to your child on what is good and what is hurting them. They need to understand that the problems that your child is having are not due to deconditioning but to the nature of the illness. If you are fortunate to find someone knowledgeable about CFS and willing to listen and work with you, this may be another route to getting a little exercise.

For some people exercising can be of great benefit, while for others, it can cause them to melt into relapses. Our recommendation is to encourage as much activity as can be tolerated. Walking, sports where breaks can be taken frequently, shopping, swimming are all examples of activities that have been tolerated by some children with CFS.



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The tolerance of these treatments varies from individual to individual.

David Bell, M.D.
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<http://www.wicfs-me.org/wicfs-5.htm>

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Media coverage of the PACE study created the false impression that CFS is potentially correctable with a disciplined approach to exercise, goal setting, and stress reduction techniques. The reporting reflected the bias of the paper's authors, who went out of their way to lend truthiness to the idea that persons diagnosed with CFS are depressed and/or lazy. The study showed that after 1 year of exercise support, CFS patients could walk about 70 feet further than untreated CFS patients. That the groups managed to walk only three football fields in length is the real news here.

When the false impression gained wide publicity, it added an element of danger to the care of CFS patients. Physicians who encourage CFS patients to exercise beyond their capacity can further damage the patients' health. CFS patients and the experienced physicians who treat them are happy to share their knowledge on this subject.

Reporters who dig deeper into the CFS story will find rich content of interest to the general public; they will generate valuable discussion and heartfelt expressions of thanks from the patient community; and they will find broader implications concerning the medical profession's paradigm for the care of chronic illness in general.

The public should know that physicians who treat patients with CFS recently revised how cases of CFS should be defined. The public should know that CFS patients can suffer from any combination of infectious, toxic, immune, neurohormonal, neurocognitive, or nutritional imbalance. Mechanisms of illness include genetic susceptibilities, toxic exposures, energy deficits, poorly controlled immune responses, loss of neuropeptide regulation of immune defenses, blood volume and blood flow, differences in gene expression following exercise, excessive oxidative stress, chronic inflammation, and more. CFS is a poster child for a systems biology approach to chronic illness.



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Scientific controversies, thrilling detective work, environmental mysteries, stirring testimonials, intellectual challenge, and oceans of gratitude await journalists and others who want to help the public understand the real CFS story and its broader implications.

Keith Berndtson, M.D.
Park Ridge, IL

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The one symptom that distinguishes CFS from other conditions is poor exercise tolerance. Formerly enjoyable physical activities become exhausting, and even after modest exercise the individual with CFS is fatigued for more than a day. This poor exercise tolerance, which has been identified as a disturbance in energy production and utilization by the body, is related to defects in the energy producing machinery of cells in the brain, muscles and other tissues.

Poor cellular energy production may also explain why chronic fatigue sufferers experience nervous system problems. CFS patients have poor cognitive function, can't concentrate on tasks and have brain biochemical disturbances that are revealed by SPECT scan.

Physiologists and medical scientists who have studied CFS find that the muscle cell mitochondria (the cells' energy furnace) of the individual with CFS are changed in shape and function from those of people who don't have this illness. CFS sufferers' mitochondria are swollen and have less energy-production ability, which may explain their fatigue and poor exercise tolerance.

In essence, a person who suffers from CFS is unable to support aerobic metabolism (metabolism in the presence of oxygen) effectively. His or her cells, after even minor stress, begin to produce energy in the absence of oxygen. Called anaerobic metabolism, this condition builds up acid debris in the cells, causing cells to become "poisoned" and reducing energy efficiency and function of the tissue or organ.

One body system that's highly dependent upon proper energy production and utilization is the immune system, the set of specialized cells which help the body defend against disease.

The white blood cells of the immune system are active metabolizers, and debilitation of their mitochondria by conditions such as poisoning can result in poor immune function.



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Poisoning of the white blood cells' mitochondria may account for the immune abnormalities in the CFS patient.

Jeffrey S. Bland, Ph.D.

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Research from the “organic school” identified many pathophysiological abnormalities in patients with ME/CFS resulting from dysfunction in a number of vital control systems of the body such as the central nervous system, the autonomic nervous system, the endocrinological system and the immune system.

The attitude of the “psycho-social school” continues to be to largely ignore this research. It seems they can only maintain their hypothesis by discouraging the search for an organic basis and by denying the published evidence, which they are certainly doing.

This unseemly battle of ideas has been settled politically by proclamation and manipulation, not by science, and not by fair and open means.

CBT and GET appear to be based on the rationale that patients with CFS/ME have “faulty” belief systems concerning the “dangers” of activity, and that these aberrant beliefs are significant perpetuating factors.

If CBT to “correct” these “false” beliefs can be combined with a graded exercise programme to re-condition these patients, it is virtually promised that a significant proportion of them will improve both their attitude and their physical functioning, and thus cure their illness. Using CBT, patients are therefore to be challenged regarding their “aberrant” thoughts and expectations of relapse that the “psycho-social school” psychiatrists believe affect symptom improvement and outcomes.

Cognitions concerning fatigue-related conditions are to be addressed; these include any alleged “over-vigilance to symptoms” and reassurance-seeking behaviours, and are to be dealt with using re-focusing and distraction techniques. It is when a therapy such as CBT begins to interfere with the natural warning systems, of which both pain and fatigue are a part, that the increased risks arise. In particular, musculo-skeletal pain and fatigue have essential function in modulating activity when the body is in a state of disease as in ME/CFS.



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NICE [National Institute for Health and Clinical Excellence in the UK], however, recommends over-riding this essential safety-net, thus the risk of serious harm is increased in this situation of simultaneous activity and symptoms denial. This will become a more serious risk in patients with more severe ME/CFS.

The Guideline does not indicate how the clinician can tell whether patients' beliefs concerning their symptoms are aberrant and/or when the symptoms accurately point to the underlying state of the disease process.

Dr. Bruce Carruthers, M.D., CM, FRCP(C)
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The whole idea that you can take a disease like this and exercise your way to health is foolishness, it's insane.

The most important thing is not to have patients do aerobic exercise. If you have a defect in mitochondrial function and you push the mitochondria by exercise, you kill the DNA.

There are a lot of diseases that have chronic fatigue. In fact, most chronic illnesses have an element of chronic fatigue. But often in those diseases, people push through it. My patients will do minimal effort, like just walking across the room, or fixing dinner and standing too long, and they're wiped out for days. And I don't know of another disease where that is the case.

The one piece of advice that I would have is, do not rationalize exercise. The rationalization of exercise goes something like this: I'm going to get up and I'm going to walk a mile on Monday and two miles on Wednesday. That doesn't work in this illness. What tends to work is: I'm going to walk around the house today, and then I'm going to answer the question the next day whether I did okay. And if I did, maybe I'll advance a little bit and ask the question: Am I all right? Sometimes it's not quite evident whether you overdid it or not at the time, but you kind of begin to internalize a sense of self -- "I think this is helping me at some deep level, I almost intuit it." When you start going from your brain thinking about exercise to feeling what it's doing, then you start to exercise correctly.



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There are several good exercises for this disease. The best exercise that I know of that's simple and inexpensive is simply to walk on flat ground. Try to do it every day if you can, but not too far. As much as you can but don't overdo it. This is best because the human being is designed to walk very efficiently. When we walk, our legs are squeezing blood, so we actually pump blood up into the heart so that you actually fill the heart. People do pretty well when they walk. You don't have to walk fast, just walk. That's very good for this disease.

Pilates is excellent for this disease, because you are going to be supine. Your energy goes up 30% when you're lying down. Just gentle types of pilates. The important thing is not get into the vertical positions.

Resistance exercise can be good, but don't use heavy weights, just use light ones. Work on range of motion with light resistance for very short periods of time. That seems to be good.

Another one is vertical inversion in water. People will just stand in water to their neck. The pressure in your body goes down as a square of the depth, so the further down you go, the pressure differential that pushes blood back up into the intravascular space and improves lymphatic drainage is excellent for Chronic Fatigue Syndrome. I think that the mobilization of lymphatic fluid is an immune modulator for these patients. They don't have to do very much. They just have to float or stand vertically for an average of 20 to 40 minutes, three times a week. It's functionally or logistically difficult sometimes for these patients to get to the pool, or the water temperature isn't right though.

What is not good is running, bicycling or significant aerobic activity. That's not good for these people. They don't fare well. Resistance training is a little better tolerated, if there isn't too much of it.

So don't be rational in exercise. Be intuitive in exercise. Don't overdo it, but do something.

Paul Cheney, M.D., Ph.D.
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<http://cfspatientadvocate.blogspot.com/2013/04/paul-cheney-lecture-march-22-2013.html>



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On one hand there is a consensus on exercise intolerance of patients suffering from Chronic Fatigue Syndrome (CFS). On the other hand there is the paper from White et al published in May 2011 in the medical journal of record The Lancet reporting that exercise could improve CFS patients' self-reported fatigue. There are not many possibilities to integrate these facts together: first, this paper is a cat among the pigeons challenging all the scientific achievements characterizing CFS of the last decades; second, this paper is an epiphenomenon in the scientific literature; or third, CFS is the victim of its complexity and then of an approximate communication.

Consensual definition (also retained by U.S. Centers for Disease Control and Prevention) of the CFS highlights the cornerstone that is fatigue (as a symptom) lasting more than 6 months. On the same way, the scientific and medical consensus defines fatigue (MeSH database, <http://www.ncbi.nlm.nih.gov/mesh?term=fatigue>) as the state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond stimuli. According to these two definitions, how exercise (MeSH database, <http://www.ncbi.nlm.nih.gov/mesh?term=exercise>), a physical activity associated to physical exertion when of usual level, could be accepted to improve CFS patients' fatigue, and then how White et al paper could be accepted as a cat among the pigeons? It's clear that we don't think this paper sweeps away by a stroke the robust literature about negative effects of exercise on CFS.

Chronic fatigue is associated with reduced exercise capacity and reduced daily activity, leading to the well-known physical deconditioning targeting among others cardiac, respiratory, muscular, and aerobic functions. Physical reconditioning, used in several medical specialties, even at very low level, is consensually accepted to improve objective (physiological functions, morbidity, mortality) as well as subjective (Quality Of Life that includes Fatigue items) criteria. Thus, reconditioning CFS patients by Graded Exercise Therapy as used in White et al study could probably improve (slightly) 6-minute walk test determinants and self-reported fatigue. But according to these well-known deconditioning and reconditioning phenomenons in sport medicine, how does this paper measure up? We don't think that White et al paper is an epiphenomenon of CFS scientific literature but we think that authors have just highlighted deconditioning experienced by CFS patients.

Finally, we think that that the main problem highlighted by the White et al paper is more linked to the approximate communication usually and often made on this very complex



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topic that is Chronic Fatigue Syndrome than to the interpretation of their results. Because the concept of fatigue is approached by so many different ways and specialties, we often forget fundamental and basic definitions, leading to cumulative approximation and distortion and justifying some regular tunings between scientists, researchers, physicians, people, media and politicians.

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The PACE study, GET/CBT idea, is a repeat of the old theory that the ME/CFS patient is imagining that they are sick and that exercise and psychological consultation will make them better.

The PACE study is flawed. The psychiatric group cannot be allowed to strangle patients and new research with their old theories.

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When exercise is individualized to the patient with CFS/ME -- using gradual, incremental steps, sometimes starting with as little as 1-2 minutes of leisurely walking (not brisk walking) -- it helps about one in two patients. That is a significant number and so is worth trying for patients with CFS/ME who have few options for effective treatment.

The other side of the data shows that a large number of patients (the other half) are not helped by exercise. Also, prescribed exercise is not intended to increase aerobic fitness, but to improve tolerance of physical exertion. Thus standard recommendations to healthy people for exercise, say 20 minutes of walking, do not apply to the CFS/ME population. Standard exercise is likely to worsen the illness.



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Also, exercise however prescribed has not been shown to be a curative intervention in any published CFS/ME study that I'm aware of. Unfortunately, that message has not been clearly conveyed in many GET studies.

Fred Friedberg, M.D.
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I believe it is erroneous to treat all ME/CFS patients similarly or to subject them to the same therapy regimen. There is sufficient evidence now, and more emerges daily, that there is high variability of symptoms amongst ME/CFS patients. Some patients may benefit from mild exercise; others will have their condition worsened by exercise.

If exercise is of benefit to ME/CFS patients, and I must emphasize the if, it would be of benefit to a subset of ME/CFS patients. Unfortunately, too little attention has been paid to the task of identifying the subsets of ME/CFS. Accordingly, until such time as the subsets are clearly defined, those studies which attempt to demonstrate a therapeutic value to a one-exercise-regimen-benefits-all, are foolish and unworthy of serious consideration.

Kenneth Friedman, Ph.D.
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The use of exercise as a treatment in CFS is never likely to solve the many problems associated with the condition. The small benefits in the CBT and GET groups in the aforementioned study still leave these patients very far away from what would be considered normal physical function. Regular light exercise may be of small benefit to some patients but it is unlikely to be suitable for all patients (especially those who are more ill) and suggesting it to all patients may cause more harm than good.

There is now some information that suggests oxidative stress and inflammation after exercise actually results in beneficial adaptations (i.e. mitochondrial biogenesis) after a period of malaise. This is clearly not the case in CFS patients, and detailed and extensive research is needed to establish the precise cause of this malaise and



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subsequently ways to treat it. This may help managing symptoms and further research should also investigate the underlying cause of the disease itself.

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There are a large number of cardiac dysfunctions that can regularly appear in an M.E. patient. Without a clear understanding of these significant problem areas it is simply indefensible and potentially dangerous to place an unsuspecting patient in a graduated exercise program. This is particularly true if the patient is not being tested in a cardiac unit.

Possibly due to the fact that some Fibromyalgia patients can be improved by a gradual increase in exercise, or possibly due to the so-called Protestant ethic that all you have to do to get better is to take up your bed and walk, some physicians have extended the concept of passive or forceful increased exercise to Myalgic Encephalomyelitis patients. This is a common and potentially dangerous, even disastrous misconception.

Doctors Jay Goldstein and Ismael Mena, using Zenon SPECT brain scans, demonstrated that the physiological brain function of an M.E. patient rapidly deteriorates after exercise. They also demonstrated that this physiological dysfunction could persist for several days following any of several stressors. The physiological dysfunction occurs whether the activity (or stressor) is physical, intellectual, sensory or emotional.

M.E. is a variable but always serious diffuse brain injury and permanent damage can be done to the M.E. patient by non-judicious pseudo-treatment.

I have yet to have examined a new M.E. or CFS patient (they are by definition quite different) who has ever had a complete cardiovascular or CNS investigation, or for that matter any complete technological examination. In other words, when physicians or insurance or government agencies make such statements concerning the theoretical benefits of graduated exercise program, they have no idea who or what the pathology is that has injured or destabilized the M.E. patient.



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In terms of the patients whose illness is consistent with the various CFS definitions, none of these patients I have ever seen have been seriously examined and as far as I am concerned, CFS is simply a missed diagnosis in which we have uncovered missed malignancies, missed MS, missed cardiac and cardiovascular disease, missed autoimmune disease. The CFS diagnosis is largely indefensible and since it can represent so many different pathologies and illnesses, it is absurd to consider a uniform treatment, whether this treatment is graded exercise or some theoretical pharmaceutical. It is essential to first discover the underlying pathologies before one considers treatment by any modality.

Byron Hyde, M.D.
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In our 2009 energy envelope paper (Jason L, Benton M, Torres-Harding S., Muldowney K., The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS, Patient Educ Couns, 2009 Nov; 77(2):237-41, PMID: 19356884), we found that the two groups of patients with ME/CFS had different outcomes on measures of physical functioning and fatigue severity after participating in a non-pharmacological intervention.

In general, those patients who exerted more energy than they had available did not improve, whereas those patients who were able to stay within their energy boundaries made significant improvements over time.

These findings suggest that when an individual with ME/CFS avoids over-exertion, maintaining an optimal level of activity over time, it might be associated with some improvements in physical functioning and fatigue. This study suggests that being overextended and going beyond energy reserves can be an impediment to improving functionality and fatigue levels.

Kindling is an explanation for what might occur when patients with ME/CFS overexert themselves and deplete energy reserves. The kindling hypothesis suggests that once this system is charged, either by high-intensity stimulation or by chronically repeated low-intensity stimulation, activities that involve going beyond energy reserves might enhance an already high level of arousal.



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In a sense, patients with ME/CFS might have this type of cortical excitability that might be due to kindling, and then when they go beyond their energy reserves, the kindling produces high arousal that has implications for the hypothalamus, the autonomic nervous system, as well as the immune system.

Leonard A. Jason, Ph.D.
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You can overdo exercise and relapse (it's in the diagnostic criteria for the illness, after all). The exercise physiology group at the University of the Pacific Fatigue Lab presented data at the IACFS/ME conference on next-day decreases in exercise capacity after an exercise stress test. It's a great model, one that we too use in our studies using formal exercise physiology lab studies to ground our work on mediators of persistent illness.

You can recondition to the point where you can do more if you are careful not to exceed your energy limit, something that can be determined using formal exercise testing (knowing the VO₂ max and aerobic threshold). But if you push beyond the limit you will experience a relapse.

We are completing a study to understand just why that happens in ME/CFS and in Gulf War illness. We have mapped out the cascade of events looking at gene activation patterns of more than 30,000 genes before, during, and after a short "push through" exercise challenge that averaged 8 minutes. It is very clear that the challenge of exercise kicks off a marked inflammatory reaction, which in turn impacts dozens of pathways - autonomic, immune, endocrine, pain, oxidative stress, intracellular metabolism, cell signaling. That patient centric concept of an energy envelope is certainly validated by our work. The use of exercise in the treatment of CFS and GWI should understand these principles.

Having said that, yes, exercise can be helpful, particularly in patients that have had other biologic aspects of the illness addressed in a meaningful way: autonomic, immune, sleep, pain, etc. Then a careful program can be designed that incorporates rest periods after relatively small efforts, and can be even more precise if the clinician has the benefit of an exercise physiologist or physical therapist with the ability to



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measure the exercise physiology parameters. A well informed physician empowers the patient by respecting their experiences, counsels the patients in coping strategies, and helps them achieve optimal exercise and activity levels within their limits in a common sense, non-ideological manner.

Nancy Klimas, M.D.
Professor of Medicine, Psychology, Microbiology and Immunology
University of Miami Miller School of Medicine

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The PACE study authors have written their case definition to include both people with major depressive disorders and patients who clearly have received an insult to their immune systems and are depressed because they can no longer do things that they used to.

Andreas Kogelnik, M.D., Ph.D.
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<http://www.nytimes.com/2011/03/08/health/research/08fatigue.html>

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There are multiple publications describing the progressive cardiomyopathy of ME/CFS. This ME/CFS cardiomyopathy is treatable with appropriate long-term antiviral therapy (Lerner et al, Virus Adaptation and Treatment, 2010). ME/CFS patients, during recovery, are advised to be active, but not to increase their heart rate above 100 beats per minute. Any greater rate worsens ME/CFS.

Martin Lerner, M.D.
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We have gene expression data in our Journal of Pain paper (Light AR, White AT, HUGHEN RW, LIGHT KC. Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. J Pain. 2009 Oct;10(10):1099-112. PMID: 19647494) that matches behavioral data from



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CFS patient that indicates that patients with CFS have negative consequences following 25 minutes of even very moderate exercise that lasts at least 48 hours. It may last much longer than this, given the information we have obtained from patients.

We have replicated these findings in a larger sample, and hope have the article on this published soon. We would like to stress that these gene expression changes are NOT found in normal control subjects with moderate, or even nearly maximal exercise, and are not seen in fit people, even with extremely intense and long lasting exercise.

Many of the gene expression changes are in the genes that detect normal levels of metabolites produced by exercising muscle. The abnormal gene expression increases indicate that the body perceives the mild exercise as extreme, and is reacting in a particularly extreme way. This leads us to believe that CFS patients bodies cannot detect and react to exercise in a normal way, and therefore, cannot protect itself from the demands of even mild exercise.

Another consequence of the gene expression changes observed is that CFS patients are "punished" for mild exercise by enhanced muscle pain and other symptoms associated with CFS that last at least 48 hours, and mostly likely much longer. This punishment would have the expected effect of making patients fearful (both cognitively and unconsciously) of performing similar exercise and could lead to serious aversion to all forms of exercise.

In our to be published paper, we have gene expression evidence that there may be a subgroup of CFS patients that might be more likely to benefit from exercise, while the majority probably will not. However, this hypothesis remains to be tested and may be false.

From the patients we have observed, it appears that CFS patients who are able to exercise regularly do benefit in their ability to be more active, but still suffer from major symptoms of fatigue and muscle pain that are not much different than when they did not exercise. In other words, they are more functional, but suffer just as much as previously.

There is a potential for harm in CFS patients following exercise, as we have observed (in the paper you describe below, and in our gene expression paper) that antiinflammatory cytokines are increased following moderate exercise, which could leave patients open to infectious diseases, and the development of neoplasms.



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Overall, I believe the exercise can help a selected group of CFS patients, and if very carefully administered, by a trained specialist who understands the great limitations, perhaps with feedback from gene expression studies. However, I seriously doubt that the majority of CFS patients will show much benefit from exercise, and that many may avoid exercise at all costs, if placed in an inappropriate exercise program.

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Our literature review article (Twisk FN, Maes M. A review on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. *Neuro Endocrinol Lett.* 2009;30(3):284-99. PMID: 19855350) shows that exertion and thus GET most likely have a negative impact on many ME/CFS patients. Exertion induces post-exertional malaise with a decreased physical performance and aerobic capacity, increased musculoskeletal pain, neurocognitive impairment, “fatigue,” weakness and a long-lasting recovery time.

This can be explained by findings that exertion may amplify pre-existing pathophysiological abnormalities underpinning ME/CFS such as inflammation, immune dysfunction, oxidative and nitrosative stress, channelopathy, defective stress response mechanisms and a hypoactive hypothalamic-pituitary-adrenal axis.

We concluded that it is unethical to treat patients with ME/CFS with ineffective, non-evidence based and potentially harmful “rehabilitation therapies” such as CBT/GET.

http://www.theoneclickgroup.co.uk/documents/ME-CFS_docs/Twisk%20Maes%20CBT.pdf

In 2006 the Belgian National Health Care Institute (Ministry of Health) evaluated the efficacy of CBT/GET in treating ME/CFS at the Belgian University CFS Reference Centers that were installed by the Ministry of Health in 2002. Hundreds of ME/CFS patients had been treated by the Belgian CFS Centers using a strict CBT/GET program.



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Based on the results obtained, the Minister of Health had to admit in the parliament that CBT/GET interventions at those CFS Reference Centers are no curative treatments (Belgian House of Representatives, 2007). But there is more. I analyzed the data of the report of the Ministry of Health. The results are shocking.

Treatment with "CBT/GET" deteriorates many patients. Up to 50-55% of all patients showed a worsening in their daily (work + leisure) activities. The VO2max worsened in up to 46-86% of the patients. The exercise tolerance (MET) worsened in 43-63% of the patients. Thus, by means of objective measurements, most patients deteriorate by CBT/GET treatments. Also the self-rating scales deteriorated in many patients: fatigue (deterioration in 23-50% of the patients), concentration (32-48%), motivation (33-80%), pain (31-33%), mental health (39-52%), anxiety (37-48%), depression (37-52%), somatic complaints (33-56%), social functioning (29-41%), physical functioning (29-50%), and quality of life (15-52%).

This proves that CBT/GET is not an evidence-based treatment and that it induces adverse effects in many patients. This is in sharp contrast to the fact that treatments should be designed to minimize pain, anxiety, discomfort, etc. But it is in line with previous patient inquiries in the United Kingdom, Scotland and the Netherlands showing that CBT/GET deteriorated the condition in 40-60% of the patients (Action for ME, 2001; CFS/ME Working Group, 2002; Action for ME, 2007; Koolhaas et al., 2008).

Although the Ministry of Health and the CFS Centers are aware that their treatments worsen the conditions of many patients they continue the same CBT/GET treatments in order "to train the patients to think about the psychological factors that may maintain and cause the complaints."

Notwithstanding the fact that the Ministry of Health and the CFS Centers know that their treatments are not evidence-based and deteriorate the condition of many patients, they pretend in official decrees and in "scientific" papers that "CBT/GET is the only evidence-based treatment that has a significant efficacy in ME/CFS." This is a fraud.

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*



Paradigm Change

The PACE trial provided evidence that 31%, 41% and 41% of subjects (Table 5) reported a positive global benefit to adaptive pacing, CBT, and GET, respectively. This meant that 69%, 59% and 59% found no global improvement or a negative change in their responses after 52 weeks of the trial. The authors concluded that CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome, but APT is not an effective addition.

The authors of this paper have advocated therapies which only appear to only mildly benefit between 30 to 40% of ME/CFS subjects yet provide no ability to determine which of the patients may benefit from such therapy.

The authors are obliged to define those subjects who may actually benefit from this treatment method and not imply that the treatment should be used on all subjects.

Treatment of all ME/CFS patients with a treatment that only assists only 30-40% of them would impose a considerable cost to the public health costs and only act to alienate many patients as is evident by the objections from patient groups to this treatment method.

In their study protocol paper, White et al (2) describe their treatment as “Rehabilitative”. The Oxford dictionary defines “rehabilitate” as “to restore (someone) to health or normal life by training and therapy after imprisonment, addiction, or illness:”. The return to normal health is obviously not occurring in this study population and therefore we would contend that the word “Palliative” is a more adapt term for use in this or other trials involved in ME/CFS patients using these methods. Palliate is defined as “to make (a disease or its symptoms) less severe without removing the cause.”

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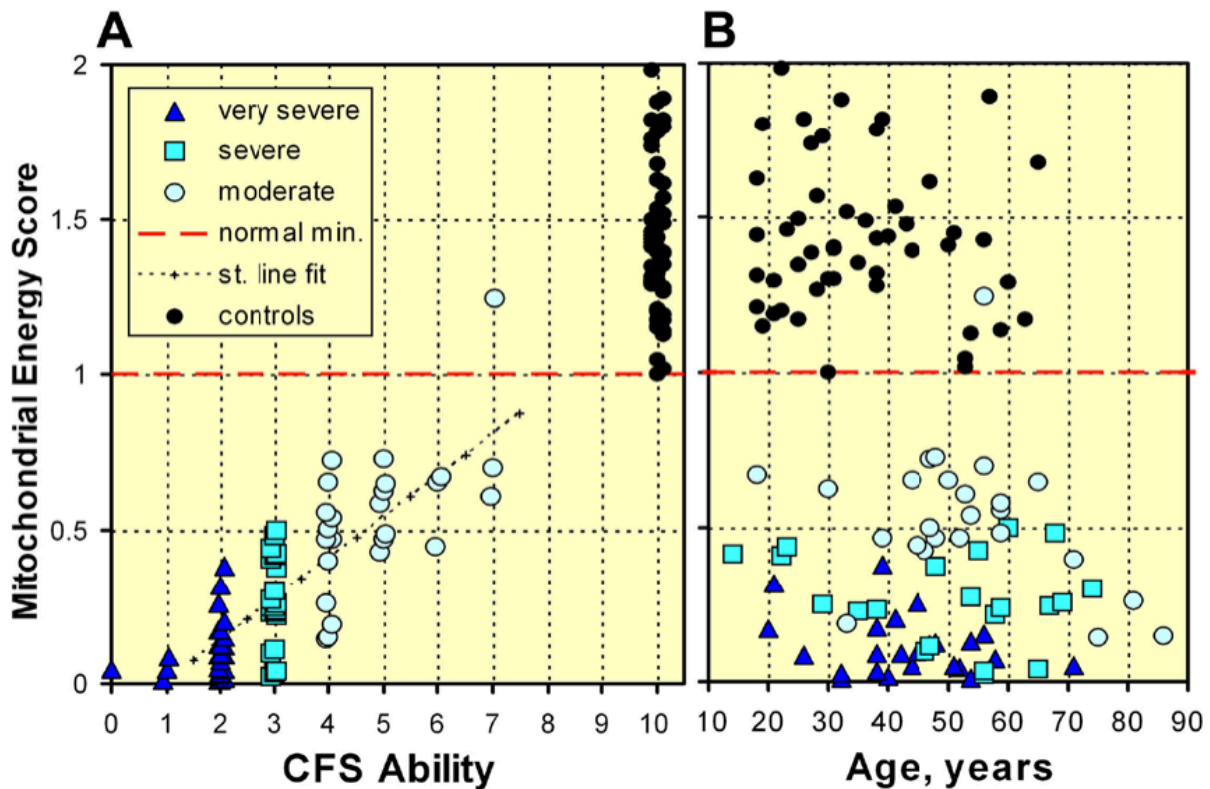
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Neil McGregor Ph.D.
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I am a doctor with a special interest in treating chronic fatigue syndrome and have treated some thousands of patients over the last thirty years.

What characterises chronic fatigue syndrome is poor stamina and delayed fatigue. My view is that these are symptoms of poor mitochondrial function and indeed I published on this subject in 2009.





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What this study showed is that those patients with the worst levels of energy had the worst mitochondrial function tests and vice versa.

The point here is that fatigue is just the symptom. If patients are improved by exercise, then by definition they do not have chronic fatigue syndrome.

Therefore it is self evident that graded exercise therapy will not be a treatment for chronic fatigue and indeed it is my experience that graded exercise almost invariably makes these patients worse.

Sarah Myhill, M.D.
Wales, UK

*

What the exercise physiology studies have shown is that in CFS, if you exceed your anaerobic threshold, you are endangering yourself and your wellness. So if you're going to do exercise, it needs to be sub-anaerobic threshold. This is one of the reasons that I always measure the anaerobic threshold, so I can always tell the patient exactly where to exercise.

It is clear that a certain portion of the disability is related to deconditioning, probably about 15%. You can condition yourself by exercise given in a safe and controlled environment. What I usually use is a very very slow rehabilitation program that actually starts with stretching and then advances to resistance weight training. The last thing we add is aerobic exercise.

If you just take a note to the rehab center, they'll always start with the treadmill, which actually makes people worse.

Daniel Peterson, M.D.
Incline Village, Nevada

<http://vimeo.com/30567445>

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Paradigm Change

I don't doubt that properly graded exercise can improve physical conditioning to a degree, but my experience with many hundreds of persons is that the degree of improvement obtainable is most often quite limited. What we have seen many times is that persons who push past their limits typically suffer a prolonged post-exertional flare-up of symptoms. We see a similar pattern of post-exertional flare-up with ME/CFS and with moderate to severe fibromyalgia as well.

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*

As an epidemiologist, I believe that the conclusions reached from British studies, arguing that Graded Exercise Therapy (GET) and Cognitive Behavioral Therapy (CBT) are beneficial to improving the illness status of ME/CFS patients, are deeply flawed and of potentially great harm to ME/CFS patients.

The main problem of these studies is that the criteria used for the selection of the patient samples involved heterogeneous groups of patients, many of whom had diagnoses of major depression rather than ME/CFS. It has long been known that both GET and CBT are beneficial to patients with depressive disorders. However, by contrast, post-exertional malaise is the hallmark symptom of ME/CFS, and patients with this disorder tend to exceed their capacity for physical exertion and subsequently relapse in contrast to the problem of depressed patients getting too little exercise.

Moreover, CBT can be useful in coping with a variety of chronic illnesses that currently have no cure. But it is crucial to understand the central difference between learning how to better live with an illness that greatly diminishes one's quality of life and the assumption that CBT can improve the actual illness, which it cannot.

Judith A. Richman, Ph.D.
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*



Paradigm Change

The disappointing results for adaptive pacing therapy (APT) in the PACE trial (1) do not reflect the feedback from the majority of published patient surveys, including ours (2), where pacing was reported to be one of the three most helpful strategies in managing ME/CFS.

The likeliest explanation is the difference between APT and the form of pacing advocated by most of the patient support groups around the world. Our version of pacing is evidence-based so it does not require patients to function well below their ability and adhere to the 70% rule, an important component of APT. It is based on clinical experience dating back to the 1950s and supported by several controlled trials showing that pacing limits post-exertional exacerbations and improves functioning over time (3). More significantly, it avoids the documented immunological and metabolic abnormalities following over-exertion (4) which are increasingly recognised as a contra-indication for graded exercise therapy (GET).

The fact that the findings of the PACE trial could result in pacing being removed as a treatment option within the NHS is just one of many concerns. The exaggeration of the outcomes, especially in the media (5), deserves to be challenged, particularly as the findings from the trials on GET are inconsistent with almost every patient group survey and audit conducted.

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Charles Shepherd, M.D.



Paradigm Change

Bucks, England

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Assessment of use of exercise as a therapeutic modality must begin with understanding the maximum delivery of oxygen (VO₂ max) and the level of oxygen delivery at which not enough oxygen can be delivered to mitochondria to keep burning sugar efficiently as a fuel (anaerobic threshold). These measures, readily obtained in a standard pulmonary lab during stress testing, provide insight to baseline exercise capacity; each impacts on the exercise prescription. Age matters here, as VO₂ max of 24 ml/kg/min is indicative of severe disability in a 24 year old but the same disability rating is reached in a 60 year old at 16 ml/kg/min. Anaerobic threshold of 50% of VO₂ max will prevent a 30 year old from achieving much benefit from efforts to use aerobic (i.e. delivering oxygen) exercise. Similarly, delayed recovery from normal activity (aka “push-crash” or “post exertional malaise”) will occur at anaerobic thresholds under 60% of those older than 60.

One cannot neglect the concept of glycogen storage potential here, as forced exercise beyond consumption glycogen reserves -- as is invariably seen in low anaerobic threshold patients being told “No pain, no gain” -- simply means that gluconeogenesis will occur, creating negative nitrogen balance. Exercise in these patients is “all pain and never any gain.”

In the presence of significant tissue inflammation, as shown by levels of T regulatory lymphocytes (CD4+CD25+) less than 14, the level of anaerobic threshold is functionally reduced by another 25-33%.

In patients with significant capillary hypoperfusion, as is commonly seen in CFS, manifested by C4a levels over 10,000 and lactate over 1.29 seen on magnetic resonance spectroscopy, the anaerobic threshold is further reduced by another 25-33%.

Simply recommending aerobic exercise in CFS is illogical. One must understand the individual’s physiology before telling anyone that exercise is indicated.

Ritchie Shoemaker, M.D.
Pocomoke City, MD

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Paradigm Change

Where I have real reservations about the trial concern what was not said rather than what they do say and the implications that follow from recommending exercise as treatment for ME/CFS without fully explaining what the results of the study really show. Walking for 6 mins at 2-2.5 mph is something even the very sick patients we see could actually do but this does not mean they are able to take on exercise in the traditional sense. If they were cardiac patients, such results would be interpreted to indicate that they would likely benefit from a heart transplant.

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*

I would entirely endorse this carefully worded critique of the claims for GET and CBT. Along the same lines, I would stress that the studies could be faulted by a) possibly including cases of "chronic fatigue" that were not true ME, but were possible depression and b) confusing the issues by combining CBT with GET. The major point that the alleged improvements were clinically pretty insignificant is crucial. Finally, the basic issue is the lack of applicability of any of this to severe cases.

You might take a clutch of severe chronic asthmatics and subject them to GET. As long as none of them had an attack and died you would end up with some slightly fitter asthmatics at the end of the six months. No one would dream of applying this to someone in the middle of a severe attack!

Yet this is how the proponents of GET behave. I am continually having to protect children with severe ME from court orders to compel hospital admission and compulsory exercise programmes. When I am unsuccessful the result is invariably that the young person is made much worse. I am willing to accept that relatively mild cases of stable convalescent ME can get a bit fitter with a gentle exercise programme as long as they don't overdo it. In my experience with young people, the main challenge is to actually restrain them from doing too much so I have hardly ever seen the need to "prescribe" exercise for them.

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*

Since 2005, the MRC has funded two large clinical trials of cognitive–behavioural approaches for ME/CFS, at a cost exceeding £3 million. The first of these (the FINE trial 1) reported that “pragmatic rehabilitation” for severely affected patients improved fatigue in the short term compared with GP treatment as usual, but had only a small, non-significant effect after one year. The second (the PACE trial 2) has now reported modest improvements in some ME/CFS patients after cognitive behavioural or graded exercise therapy; a “clinically useful difference” in the primary outcomes of fatigue and physical function after one year occurred in 45%, 59% and 61% of the standard medical care, cognitive behavioural and graded exercise groups, respectively.

Neither of these expensive trials has established cognitive–behavioural approaches as convincing, core treatments for most patients with ME/CFS. Indeed, when their results are placed side-by-side with the most recent Cochrane review 3 and the most comprehensive meta-analysis 4 to date (which reported a small–moderate overall effect size from 13 diverse trials), it is clear that psychosocial interventions have only an adjunctive role. The situation is therefore akin to that in other chronic illnesses, such as multiple sclerosis 5, where these non-specific approaches help with managing symptoms and promoting coping, but form only a small part of the clinical and therapeutic armoury required to address the underlying disease processes.

We conclude therefore that academic interest (and funding) should now focus on biomedical investigation to arrive at specific therapies for this debilitating illness.

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*

I consider that the recommendation of CBT and GET as blanket treatments of “clinically excellent” first choice is extremely dangerous to patients.

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<http://www.investinme.org/Article-361%20Statements%20of%20Concern%20-%20CBT-GET%20JR%20Feb09.htm>

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The belief that exercise is a treatment for ME/CFS is just plain wrong. The face validity of trials such as the PACE must be called into question if the majority of real patients do not respond similarly to study participants.

It is a laudable goal for anyone chronically ill with ME/CFS or otherwise to maintain the best fitness possible. Exercise improves cardiovascular health, mental health and maximizes the ability of patients to do necessary daily activities.

However, in my 10 years in a dedicated ME/CFS practice, I hear over and over the despair engendered by repeated, unsupervised attempts to increase exercise.

We are experimenting with heart rate, heart rate variability and lactate curves as tools to help patients identify their individual optimal exercise frequencies and intensities and to objectively measure whether exercise programs are helping or hurting.

It remains a challenge to improve fitness and quality of life while respecting the energy envelope limits of ME/CFS. More research is desperately needed.



Paradigm Change

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Our lab has focused on functionally characterizing CFS/ME patients.

After completing over 1,110 cardiopulmonary exercise tests for a clinical trial in CFS/ME at 12 different locations across the country, we looked at the baseline data and found that all of our patients achieved an oxygen consumption level of 36-76% of predicted values (VanNess, et al, 2003). Half the patients in the study were in the moderate to severe impairment category based on American Medical Association Guidelines for the evaluation of permanent impairment.

Of particular interest was the delayed recovery response the patients routinely reported. This led us to test patients on consecutive days.

Patients are consistently unable to reproduce test results and show reduced work efficiency in the post-exercise state. Our initial findings were confirmed by a group in the Netherlands (Vermeulen, et al 2010).

The symptom of post-exertional malaise (PEM) is a real and measurable finding. Our patients report that it takes several days and sometimes weeks to recover from an 8-12 minute bout of exercise. This is not a normal response to an activity that for healthy people makes them feel better.

The symptom of PEM must be taken into consideration when designing any type of exercise program. If there is metabolic dysfunction, asking a patient to exercise aerobically will not work but will make them worse.

Staci R. Stevens
Founding Executive Director
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*



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A literature review looking at severe fatigue in cancer patients also noted that counseling and exercise can be helpful in cancer patients (Cancer-Related Fatigue: A Practical Review). Using the line of reasoning applied by some to the PACE study, this would also suggest that cancer is all in people's minds.

Of course, this is simply an absurdity that points to the simple fact that for most severe debilitating diseases, emotional support and coping skills can be helpful along with maintaining conditioning.

In chronic fatigue syndrome, people are facing an energy crisis so they can only walk or exercise to a certain point, beyond which they crash and burn. So you only want to exercise "as able." This means listening to your body and seeing what feels comfortable.

On the other hand, if you don't exercise at all, your body has a "use it or lose it" approach to efficiency, and you'll decondition.

So basic common sense says that for cancer, chronic fatigue syndrome, multiple sclerosis (which doctors also used to believe was all in people's minds, calling it "hysterical paralysis"), and any severe disease, it is helpful to get emotional support, coping skills, and exercise as able.

The problem occurs when a form of cognitive behavioral therapy is used that includes beating people over the head with the misguided belief that the illness is not real. This then changes from teaching coping skills to being abusive.

Jacob Teitelbaum, M.D.
Kona, HI

*

Over the years I have seen many patients with a diagnosis of CFS/ME. The outstanding feature for most is intolerance to more than a minimal amount of exercise, with risk of serious relapse if the ability envelope is exceeded.

It seems that these patients are on a knife-edge, and each needs careful assessment, with any recommendations for exercise being cautiously managed by medical professionals experienced in this illness. Pushing the boundaries beyond the comfort



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zone does not work. Words such as “training,” “getting fit,” “aerobics” etc are totally inappropriate.

Most patients are motivated and keen to improve, but usually know their limitations well when it comes to exercise. We need to listen to our patients, and work together as a team, structuring any recommendations according to what is individually possible, without causing escalation of symptoms heralding relapse.

Rosamund Vallings, MNZM, MB BS
Auckland, New Zealand

*

When working with children and teens living with ME/CFS, I meet with the child and available family members at the first and at later sessions, as appropriate. A primary goal is to learn (1) from the youngster what symptoms s/he is experiencing and her/his priorities for treatment focus, (2) from the parents their concerns and goals, and (3) from siblings their concerns and questions about their sibling’s illness.

We also discuss the critical concepts about the variable nature of ME/CFS and the importance to the sibling ill with ME/CFS of pacing activities (physical, intellectual, social) to keep expenditure of his/her energy within an “envelope” of safe functioning. I also use the concept of battery size to describe available energy: the person with ME/CFS has an AAA-size battery supply while most healthy people have a D-size battery. The youngster gains practice in deciding when and how much energy to expend (or not) if s/he wants to reduce likelihood of symptom exacerbation. Rigid programs/schedules for increasing “activity” can be harmful physically and disrespectful of the youngster’s experience of his/her symptoms.

Using simple forms, the youngster (with parent’s help if needed) creates an activity record of energy expended and physical/cognitive symptom experiences.

In subsequent sessions, the youngster’s experiences with pacing and parents’ observations are reviewed and used to guide next steps. Hopefully, over time, the youngster will become more adept at monitoring symptoms and energy expenditure.

It is very important to inform the youngster’s school about the child’s ME/CFS so as to access the educational accommodations s/he is entitled to receive. A collaborative



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approach is critical to support the young person's education at a pace and in a format compatible with his/her health status.

Constance Van der Eb, Ph.D.
Lake Bluff, IL

*

Exercise requires an increase in the rate of production of ATP (adenosine triphosphate) in the mitochondria (cellular power plants) of the cells of the skeletal muscles and the heart muscle, because ATP supplies the energy to power muscle contractions.

Unfortunately, there is abundant evidence that people who have ME/CFS suffer from dysfunction of their mitochondria, among many other biochemical and physiological abnormalities.

The mitochondrial dysfunction manifests among other ways as elevated oxidative stress. Oxidative stress results in damage to lipid membranes, proteins and DNA in the cells.

When a person who has ME/CFS undertakes significant exercise, their dysfunctional mitochondria are forced to try to produce ATP at a higher rate. The resulting increase in oxidative stress likely produces additional damage, and the time required for repair of this damage may be at least partly responsible for the postexertional exhaustion and malaise that is a hallmark of ME/CFS, lasting for a day or in some cases much longer after significant physical exertion.

This is not to say that some exercise is not beneficial and in fact needed. It helps to maintain several body organs and systems, including the muscles, the heart and circulatory system, the lymph system, the digestive system, the vestibular system, the joints, and others. The key is that the amount of exercise that is beneficial but not deleterious is very much an individual property of each patient and their current condition. This amount is best determined by the individual patient, starting with a small amount, and waiting until the next day to see how well it was tolerated, before increasing the amount by another small increment, waiting again to gauge the effect, and so on. It should be recognized that ME/CFS is characterized by relapses, which may decrease the amount of exercise that was previously found to be tolerable.



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In my opinion, efforts by other parties to increase the amount of exercise that an individual patient undertakes should be entered upon with a great deal of caution, and should be done in a cooperative manner with the patient, following this procedure.

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*

The Stevens protocol is a two-day series of maximal, cardiopulmonary exercise tests that challenge the physical working capacity of a patient with CFS/ME. The test-retest design is intended to determine physical working capacity when the patient is in a rested and non-exacerbated state on day one of the tests. The stress of doing the exercise test typically exacerbates symptoms and produces a subsequent “flare-up” typical of post-exertional malaise. The second day of exercise testing is identical to the first. Any changes in the cardiac, pulmonary, metabolic or workload observed on the second day compared to the first objectively informs of the systems that may be impaired in the post-exertional state.

There are a number of advantages in this design:

1. Maximal effort on both exercise tests is important and standardized objective criteria are used to judge effort. When maximal effort is given by the patient on both tests, the comparison of performance on the first day compared to the second allows each subject to serve as their own control.
2. The effects of detraining often evident in CFS/ME are precluded in this design.
3. The failure to reproduce performance on cardiopulmonary exercise tests may be a unique finding to CFS/ME and measures the symptom of post-exertional malaise. There is strong support from scholarly literature of a number of pathological conditions that repeated exercise tests produce nearly identical cardiac, pulmonary and metabolic responses.
4. The findings from the exercise testing may be used to support claims of physical disability in job-related litigation.

Mark VanNess, PhD
Pacific Fatigue Laboratory



Paradigm Change

Department of Sport Sciences
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CBT is a psychological treatment. Its application in what is certainly an organic disorder is basically irrational. Its putative mode of action is based on the proposition that patients with ME/CFS feel unwell because they have an “abnormal illness belief,” and that this can be changed with CBT. It has never been proven to be helpful in the majority of patients with ME/CFS.

GET comprises a regime of graded exercise, increasing incrementally over time. A number of patient surveys have shown it to be, at best, unhelpful, and at worst, very damaging. Its application is counterintuitive, particularly when one of the most debilitating and well recognised symptoms of ME/CFS is post-exertional malaise, which can put some patients in bed for days after relatively trivial exertion.

Dr. William Weir, FRCP
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Cognitive Behavioral Therapy, (CBT) and Graded Exercise Therapy (GET) were developed as support therapies for those with primary depression who are otherwise in good health. It is well known that appropriately diagnosed M.E. and CFS patients suffer from physical infectious symptoms including sore throat, lymphadenopathy, low grade fever, night sweats and other flu like symptoms which would make it irrational to even suggest the use of CBT or GET as actual treatments.

Just as doctors would never prescribe such treatments for strep throat or Hepatitis C, it is irresponsible to suggest these methods would be effective for patients with ME and CFS. In addition, research physiologists have shown that patients suffer from relapses of their illness when forced to exercise against their will or when told to “push through” their illness.

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<http://www.prohealth.com/library/showarticle.cfm?libid=15970>

CFS AND EXERCISE INTOLERANCE

PROBLEMS WITH THE PACE STUDY: A BRIEF CRITIQUE

THE STUDY:

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M; PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 2011 Mar 5;377(9768):823-36. PMID: 21334061

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www.pacetrial.org/trialinfo.html

<http://www.meactionuk.org.uk/FULL-Protocol-SEARCHABLE-version.pdf>

STUDY BACKGROUND:

This study was conducted by a team of psychiatrists in the UK between 2005 and 2010. It cost a total of 5 million pounds (\$8 million), and was funded by the UK Medical Research Council, the Department of Health for England, the Scottish Chief Scientist Office, and the Department for Work and Pensions.

Participants consisted of 641 individuals meeting the Oxford criteria for chronic fatigue syndrome (with fatigue as the only symptom, accompanied by significant disability in the absence of an exclusionary medical or psychiatric diagnosis). All subjects were age 18 or over, and they had to be well enough to be able to attend 14 or more sessions of therapy over a 52 week period.



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All patients received a lecture and a pamphlet from a medical practitioner specializing in the disease. They then were divided into four groups.

Patients in the “cognitive-behavioral therapy” (CBT) condition discussed with therapists how they could arrange their lives so that they could participate in a modest amount of activity and exercise each day. A goal was to have the amount of exercise very gradually increase over time. Topics discussed in the sessions included the importance of planning out each day’s activities in advance and sticking to that schedule as well as ways to reduce general stressors in life.

Patients in the “graded exercise therapy” (GET) condition also were encouraged to engage in modest amounts of exercise each day, and were taught how to use a heart rate monitor to make sure that they did not exceed their limitations. Again, a goal was to have the amount of exercise gradually increase over time. Patients were encouraged to engage in physical routines thought to be conducive to physical conditioning, such as doing extensive stretching before exercising.

Patients in the “adaptive pacing therapy” (APT) condition worked with therapists to monitor their condition, to make sure that they were not doing more than their bodies would allow. Their goal was to conserve energy to the extent that they were able.

Patients in the control condition received no treatment other than the lecture and pamphlet from the medical practitioner.

After 52 weeks, patients were evaluated on a number of dimensions.

The “Chalder Fatigue Scale” had patients rate their own current level of fatigue. Patients in the CBT and GET groups rated their fatigue as significantly (about 15%) lower on average than those in the APT and control groups.

The “Physical Functioning” scale had patients rate their ability to engage in a variety of activities (such as walking or climbing stairs). Patients in the CBT and GET groups rated their ability as significantly (about 10%) higher on average than those in the APT and control groups.

A “Six Minute Walking Test” gauged how far patients could walk in six minutes. The patients in the GET group were able to walk significantly (a little less than 10%) further on average than patients in the other three groups.



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Based on this, GET and CBT were deemed by the authors to be successful treatments for CFS. These therapies are currently incorporated into the NICE (National Institute for Health and Clinical Excellence) Guidelines as the only accepted treatments for the disease in the UK, and received a substantial amount of favorable media coverage in both the US and UK.

STUDY CRITICISMS:

This study has been subject to a wide variety of criticisms, some of which are included here.

Effect Sizes:

One problem is that although the large sample size meant that the findings achieved statistical significance, the actual effect sizes were quite small.

At the beginning of the study, subjects scored an average of about 27 on the 33-point Chalder Fatigue Scale (described below). By the end of the 52 weeks, patients in all the groups improved. Those in the control condition scored 24, compared to 20 in the CBT condition and 21 in the GET condition. While this was a significant difference, the magnitude of difference between groups was small. On average, patients in all the groups stated that they continued to be more fatigued than before they got sick on the equivalent of every item on the scale.

At the beginning of the study, subjects scored about 38 on the 100-point Physical Functioning scale (also described below). By the end of the 52 weeks, patients in all three groups improved. Those in the control group scored an average of 51, compared to an average of 58 in both the CBT and GET groups. On average, patients in all groups remained limited in their ability to do basic activities such as carry groceries, walk up a flight of stairs or bathe themselves.

For the six-minute walking test, patients in the GET condition were able to walk an average of 379 meters (compared to 312 at the beginning of the study). This was a significantly bigger improvement than that of the control group, who could walk an average of 348 meters (compared to 326 at the beginning of the study). However, it was still substantially less than the distance (631 meters) that healthy people aged 65+ were able to walk in six minutes in another study (Troosters T, Gosselink R, Decramer M. Six

minute walking distance in healthy elderly subjects. Eur Respir J 1999; 14: 270-274, PMID: 10515400).

Appropriateness of Dependent Variables:

CFS is a multisystemic illness with a wide variety of symptoms other than fatigue. The authors failed to incorporate that fact into their study. The reported effects centered on three variables -- fatigue, physical functioning and (for the GET condition) six-minute walking ability. For instance, cognitive functioning (a key issue in the disease) did not differ significantly across groups at the end of the 52 weeks.

The Chalder Fatigue Scale and Physical Functioning Scale are both subjective measurements. Conceivably, patients who had received 14 sessions of therapy may have been more inclined to report improvements than those who had received no therapy -- even if that wasn't reflective of reality -- because they had the underlying desire to feel their time wasn't wasted or to make it seem like the therapist had been helpful.

The one objective measurement showing an effect -- the six-minute walking test -- is not reflective of patients' lives as a whole. By definition, CFS patients' abilities are constrained less by their inability to participate in activity than by the negative effects that they experience afterwards.

For instance, one study on exercise by another group demonstrated (by having patients wear a device to track all their movements throughout the day) that patients who participated in structured exercise reduced their activity at other times to compensate. (Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. Dyn Med. 2005 Oct 28;4:10. PMID: 16255779) Conceivably, patients in the GET condition might have pushed themselves to walk fast for six minutes to demonstrate their success in the program, then spent the next day or week in bed.

Study Population:

Another group of criticisms is related to the patient population who participated in the study.



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Patients had to be able to attend 14 or more sessions at a hospital clinic. Thus, those who were severely ill with CFS (housebound or bedbound) were excluded. Whether any of the study findings might be applicable to them is wholly unknown.

The use of the Oxford definition -- which uses no symptoms other than fatigue in the criteria -- presents another problem. Fatigue is just one of many symptoms in CFS, and it is characteristic of many other illnesses as well. In particular, it is a symptom of major depression, and the PACE study did not exclude people who were depressed.

The authors reported that some of the people in the study indeed had plain depression rather than CFS. Since people with depression are known to benefit from psychotherapy and exercise, the inclusion of even a few of these individuals could have skewed the results enough to make it look like the interventions were helpful for subjects in general.

As a result of criticisms of the study population, the authors re-ran the data to determine if there were interaction effects between a) those patients who met the CDC (Fukuda) criteria for CFS vs. those who did not and b) the experimental condition (GET, CBT, APT or control). The dependent variables were the Chalder Fatigue Scale and the Physical Function Scale. They found no such interactions.

However, not finding an interaction does not mean that there is no actual underlying interaction, since it may be that insufficient sample size was responsible for the lack of significant effect. If the authors wanted to show that people meeting the CDC criteria improved more in the GET or CBT conditions than in the control condition, they should have done an analysis of main effects just on those people. The fact that they did not do this suggests that they did not have enough people who met the CDC criteria to prove that the small effect sizes were not due to chance.

The CDC definition of CFS is itself quite broad. For instance, people who do not have post-exertional exhaustion (the recognized cardinal symptom of the illness) can qualify. Especially since the authors' results were counter to more than 50 studies in the medical literature showing various negative physiological effects as a result of exercise in CFS patients, the use of a more restrictive definition would have been appropriate.

Study Implementation:



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The writeup of the study made it seem that any improvements that occurred were due to increased exercise as a result of physical therapy or psychotherapy. The instructions given to therapists suggest that this may not have been the case, however.

For one thing, subjects in the groups receiving therapy were given counseling that may have helped their condition in ways unrelated to exercise. In the CBT condition, people were encouraged to find ways to reduce stress in their lives -- conceivably allowing them to need to push themselves less hard and thus to experience physical improvements as a result of increased rest. In the GET condition, sleep hygiene skills (such as taking a hot bath before bedtime) were discussed. Since sleep is disordered in CFS, this may have helped their physical condition.

Therapists were instructed to remain sympathetic and supportive of the patients. In general, people who are having a difficult time often benefit psychologically from any sort of positive attention, perhaps especially from therapists. It could be that people who were getting GET or CBT felt emotionally better as a result of the interactions and that this affected their perceptions (but not the reality) of how they were doing physically.

Subjects in both the GET and CBT conditions were encouraged to start out with very gentle exercise (relying either on a heart rate monitor or on their physical responses) and to increase the amount very gradually. On the other hand, newly diagnosed CFS patients who are not receiving coaching tend to engage in a push/crash phenomenon -- exercising vigorously and then experiencing extended post-exertional exhaustion. Conceivably, patients in the GET and CBT conditions actually might have been exercising less on average than patients in the control condition, with their increased energy and improved physical function resulting from having pushed themselves less hard throughout the year.

Another issue concerns the possibility that GET and CBT is not implemented by other therapists in the ways that it was in the study. Therapists in this study were instructed to be particularly supportive and received in-depth training in the particular methodologies used -- for instance, with strong emphasis placed on the idea of extremely gradual increases in activity. Therapists who are less focused on clients' individual situations and who push hard for faster improvements might generate very different results.

In addition, the 14 sessions of therapy that patients received may be unrealistic in the real world, considering restraints on healthcare spending. Fewer sessions might not provide the same results.



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Reporting:

Especially when describing the study to the media, the authors and others promoting it frequently have made the results sound more impressive than they actually are. None of the groups of patients achieved a recovery to anything even close to normal levels of functioning, and the magnitude of differences between getting extensive treatment vs. no treatment were very small.

These researchers and their supporters repeatedly have made statements listing the percentage of subjects in the GET and CBT conditions who have improved, without stating the percentage in the control condition who improved.

For instance, for the Physical Function Scale, about 70% of patients in the GET and CBT conditions improved, compared to 58% in the control condition. For the Chalder Fatigue Scale, 76-80% of patients in the CBT and GET conditions improved, compared to 65% in the control condition. For participant ratings of overall global health, 41% in the GET and CBT conditions improved, compared to 25% in the control condition.

Statements such as “41% of patients receiving GET and CBT improved” thus are misleading, since the majority of those individuals would have improved without any treatment at all.

Contrast with Findings in Medical Literature

More than 50 papers on exercise intolerance in CFS patients have been published by medical researchers. These papers demonstrate a wide variety of abnormal negative physiological changes in patients, usually lasting for days (sometimes longer) after the exercise occurs.

The authors of the PACE study state that they are operating under the theory that the problems that patients have with exercise is that they are deconditioned or have an irrational fear of exercise. This is not consistent with the peer-reviewed medical literature, which shows changes related to a wide variety of physiological measures (such as inflammation and oxidative stress) that have nothing to do with muscle conditioning or exercise phobia. It also is not consistent with the observed experience of the illness, in which many extremely fit individuals become permanently bedridden overnight.



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Exercise intolerance is such a core phenomenon of the illness that a team of researchers from the University of Utah recently received an \$1 million grant from the NIH to study gene expression after exercise as a particularly likely biomarker for the illness.

<http://www.dailyutahchronicle.com/news/campus/national-institutes-of-health-funds-1-million-study-on-fatigue/>

<http://www.research1st.com/2011/09/19/light-nih/>

The idea that exercise could be an effective treatment (much less a cure) for CFS is thus counter to the ways in which the phenomenon is viewed by almost all medical professionals and researchers familiar with the illness. Putting aside the large amount of solid medical literature on the topic of exercise in CFS in favor of this flawed paper thus does not seem appropriate.

-Lisa Petrison, Ph.D.



Paradigm Change

Chalder Fatigue Scale:

33 points possible

1. Do you have problems with tiredness?
2. Do you need to rest more?
3. Do you feel sleepy or drowsy?
4. Do you have problems starting things?
5. Do you lack energy?
6. Do you have less strength in your muscles?
7. Do you feel weak?
8. Do you have difficulty concentrating?
9. Do you make slips of the tongue when speaking?
10. Do you find it more difficult to find the correct word?
11. How is your memory?

Items 1-10: Less than usual, 0; No more than usual, 1; More than usual, 2; Much more than usual, 3.

Item 11: Better than usual, 0; No worse than usual, 1; Worse than usual, 2; Much worse than usual, 3.

SF-36 Physical Function Sub-scale:

100 points possible

The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

1. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
2. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf
3. Lifting or carrying groceries
4. Climbing several flights of stairs
5. Climbing one flight of stairs
6. Bending, kneeling or stooping
7. Walking more than a mile



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- 8. Walking several hundred yards
- 9. Walking one hundred yards
- 10. Bathing or dressing yourself

Scale: Not limited at all, 0; Yes, limited a little, 5; Yes, limited a lot, 10.

CFS AND EXERCISE INTOLERANCE

MEDICAL LITERATURE

White AT, Light AR, Hughen RW, Vanhaisma TA, Light KC. 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. *Psychosom Med.* 2012 Jan;74(1):46-54. PMID: 22210239

Postexercise mRNA increases in metabolite-detecting receptors were unique to patients with CFS, whereas both patients with MS and patients with CFS showed abnormal increases in adrenergic receptors. Among patients with MS, greater fatigue was correlated with blunted immune marker expression.

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Cook DB, Stegner AJ, Nagelkirk PR, Meyer JD, Togo F, Natelson BH. Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. *Med Sci Sports Exerc.* 2012 Jun;44(6):1186-93. PMID: 22157881

The purpose of the present study was to examine cardiac and perceptual responses to steady-state submaximal exercise in CFS patients and healthy controls. The CFS + FM group exhibited an exercise response characterized by higher stroke index, ventilatory equivalents for oxygen and carbon dioxide and rating of perceived exertion, lower systolic blood pressure, and similar HR responses compared to controls.

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Jammes Y, Steinberg JG, Delliaux S. Chronic fatigue syndrome: acute infection and history of physical activity affect resting levels and response to exercise of plasma oxidant/antioxidant status and heat shock proteins. *J Intern Med.* 2011 Nov 24. PMID: 22112145

The presence of stress factors in the history of CFS patients is associated with severe oxidative stress and the suppression of protective HSP27 and HSP70 responses to exercise.



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Jones DE, Hollingsworth KG, Jakovljevic DG, Fattakhova G, Pairman J, Blamire AM, Trenell MI, Newton JL. Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study. *Eur J Clin Invest*. 2011 Jun 10. PMID: 21749371

CFS patients exhibit “profound abnormality in bioenergetic function.” When they exercise at the level of normal people, they demonstrate increased intramuscular acidosis that does not decrease normally with repeated exercise. Compared to normal people, it also takes four times as long for their pH to return to baseline after exercise.

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Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G, De Clerck LS. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *Eur J Clin Invest*. 2011 Jul 2. PMID: 21793823

CFS patients suffer from hyperresponsiveness of the central nervous system to various stimuli, including heat, mechanical pressure, electrical stimulation and histamine. Exercise worsens this tendency.

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Light AR, Bateman L, Jo D, Hughen RW, Vanhaitsma TA, White AT, Light KC. Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. *J Intern Med*. 2011 May 26. PMID: 21615807

CFS patients exhibited two different abnormal responses to exercise. Some patients demonstrated abnormal increases in mRNA for sensory and adrenergic receptors and a cytokine, resulting in fatigue or pain. A second group demonstrated abnormal decreases in adrenergic α -2A receptor's transcription. None of the normal patients in the study showed these responses, and the authors thus suggest that this finding has the potential of serving as a biomarker for the disease.

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Paradigm Change

Davenport TE, Stevens SR, Baroni K, Van Ness M, Snell CR. Diagnostic accuracy of symptoms characterising chronic fatigue syndrome. *Disabil Rehabil.* 2011 Jan 6. PMID: 21208154

Presence of just three measures (fatigue, sleep and pain) was effective in predicting exercise intolerance -- a definitional indicator of CFS status.

*

Vermeulen RC, Kurk RM, Visser FC, Sluiter W, Scholte HR. Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. *J Transl Med.* 2010 Oct 11;8:93.

CFS patients reached the anaerobic threshold and the maximal exercise at a much lower oxygen consumption than the controls, and this worsened in the second test. This implies an increase of lactate, the product of anaerobic glycolysis, and a decrease of the mitochondrial ATP production in the patients.

*

Meeus M, Ickmans K, De Clerck LS, Moorkens G, Hans G, Grosemans S, Nijs J. Serotonergic descending inhibition in chronic pain: design, preliminary results and early cessation of a randomized controlled trial. *In Vivo.* 2011 Nov-Dec;25(6):1019-25. PMID: 22021700

The authors administered the antidepressant citalopram to CFS patients and then had them perform a submaximal exercise protocol, preceded and followed by an assessment of endogenous pain inhibition. Significant negative effects were observed in all patients and the authors decided that proceeding with the study would be unethical.

*

Meeus M, Roussel NA, Truijten S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med.* 2010 Oct;42(9):884-90. PMID: 20878051

CFS patients show hyperalgesia and abnormal central pain processing during submaximal aerobic exercise.



Paradigm Change

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Meeus M, van Eupen I, van Baarle E, De Boeck V, Luyckx A, Kos D, Nijs J. Symptom fluctuations and daily physical activity in patients with chronic fatigue syndrome: a case-control study. *Arch Phys Med Rehabil.* 2011 Nov;92(11):1820-6. PMID: 22032215

The more that patients with CFS are sedentary and the better activity is dispersed, the fewer symptoms and variations they experience on the same and next day. Inversely, more symptoms and variability is experienced when patients were more active that day or the previous day.

*

Suárez A, Guillamo E, Roig T, Blázquez A, Alegre J, Bermúdez J, Ventura JL, García-Quintana AM, Comella A, Segura R, Javierre C. Nitric Oxide Metabolite Production During Exercise in Chronic Fatigue Syndrome: A Case-Control Study. *J Womens Health (Larchmt).* 2010 May 14. PMID: 20469961

CFS patients had a higher increase in nitric oxide metabolites after exercise than did controls.

*

Nijs J, Van Oosterwijck J, Meeus M, Lambrecht L, Metzger K, Frémont M, Paul L. Unravelling the nature of postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: the role of elastase, complement C4a and interleukin-1beta. *J Intern Med.* 2010 Apr;267(4):418-35. PMID: 20433584

Following exercise, complement C4a levels go up more in CFS patients than in healthy people.

*

Maes M, Twisk FN. Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways. *BMC Med.* 2010 Jun 15;8:35. PMID: 20550693

The authors describe how physiological abnormalities related to inflammatory, immune, oxidative and nitrosative pathways interfere with exercise tolerance in CFS.

*

Jones DE, Hollingsworth KG, Taylor R, Blamire AM, Newton JL. Abnormalities in pH handling by peripheral muscle and potential regulation by the autonomic nervous system in chronic fatigue syndrome. *J Intern Med.* 2010 Apr;267(4):394-401. PMID: 20433583

CFS patients displayed abnormalities in recovery of intramuscular pH, related to autonomic dysfunction, following exercise.

*

White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC. Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. *Psychophysiology.* 2010 Mar 4. PMID: 20230500

CFS patients often display negative responses to exercise, as a result of abnormal inflammatory cytokine activity.

*

Robinson M, Gray SR, Watson MS, Kennedy G, Hill A, Belch JJ, Nimmo MA. Plasma IL-6, its soluble receptors and F2-isoprostanes at rest and during exercise in chronic fatigue syndrome. *Scand J Med Sci Sports.* 2010 Apr;20(2):282-90. PMID: 19422646

CFS patients have higher levels of F(2)-isoprostanes, an indicator of oxidative stress, after exercise.

*

Van Oosterwijck J, Nijs J, Meeus M, Lefever I, Huybrechts L, Lambrecht L, Paul L. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. *J Intern Med.* 2010 Sep;268(3):265-78. PMID: 20412374

Healthy subjects are able to tolerate a higher level of pain following exercise, while CFS patients are able to tolerate a lower level of pain following exercise.



Paradigm Change

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Brown M, Khorana N, Jason LA. The role of changes in activity as a function of perceived available and expended energy in nonpharmacological treatment outcomes for ME/CFS. *J Clin Psychol*. 2010 Oct 25. PMID: 20976708

CFS patients who were within their energy envelope before treatment showed more improvement in physical functioning and fatigue compared with those outside of their energy envelope.

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VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. Postexertional malaise in women with chronic fatigue syndrome. *J Womens Health (Larchmt)*. 2010 Feb;19(2):239-44. PMID: 20095909

Following an exercise test, all the normal sedentary controls recovered quickly (within 24-48 hours) while none of the CFS patients did. Symptoms the patients reported after the test included fatigue, light-headedness, muscular/joint pain, cognitive dysfunction, headache, nausea, physical weakness, trembling/instability, insomnia and sore throat/glands.

*

Light AR, White AT, Hughen RW, Light KC. Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. *J Pain*. 2009 Oct;10(10):1099-112. PMID: 19647494

After sustained moderate exercise, CFS patients showed greater increases than control subjects in gene expression for metabolite detecting receptors ASIC3, P2X4, and P2X5, for SNS receptors alpha-2A, beta-1, beta-2, and COMT and IS genes for IL10 and TLR4. This correlated with an exacerbation in their symptoms.

*

Twisk FN, Maes M. A review on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for



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many patients with ME/CFS. *Neuro Endocrinol Lett.* 2009;30(3):284-99. PMID: 19855350

The authors discuss how the use of exercise therapy in CFS may be harmful to patients.

*

Maes M. Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. *Curr Opin Psychiatry.* 2009 Jan;22(1):75-83. PMID: 19127706

The authors review recent findings on inflammatory and oxidative and nitrosative stress (IO&NS) pathways in CFS and suggest that for these patients, exercise can be a trigger factor causing damage.

*

Sorensen B, Jones JF, Vernon SD, Rajeevan MS. Transcriptional control of complement activation in an exercise model of chronic fatigue syndrome. *Mol Med.* 2009 Jan-Feb;15 (1-2):34-42. PMID: 19015737

Mannan-binding lectin serine protease 2 (MASP2) was higher than normal following exercise in CFS patients, and this seems related to the phenomenon of post-exertional malaise.

*

Jammes Y, Steinberg JG, Delliaux S, Brégeon F. Chronic fatigue syndrome combines increased exercise-induced oxidative stress and reduced cytokine and Hsp responses. *J Intern Med.* 2009 Aug;266(2):196-206. PMID: 19457057

CFS patients have more severe and longer oxidative stress following exercise, and this may result from delayed and insufficient heat shock proteins protecting the cells.

*

Paul L, Rafferty D, Marshal R. Physiological cost of walking in those with chronic fatigue syndrome (CFS): a case-control study. *Disabil Rehabil.* 2009;31(19):1598-604. PMID: 19848558

Compared to controls walking at the same speed, CFS patients had a lower gross and net oxygen uptake and suffered a higher physiological cost.

*

Maes M, Twisk FN. Chronic fatigue syndrome: la bête noire of the Belgian health care system. *Neuro Endocrinol Lett.* 2009;30(3):300-11. PMID: 19855351

In case reports, the authors show that Belgian patients who received Graded Exercise Therapy in fact suffered from disorders of the inflammatory/oxidative/nitrosative stress pathways, including intracellular inflammation, an increased translocation of gram-negative enterobacteria (leaky gut), autoimmune reactions and damage by O&NS. They suggest that exercise was inappropriate treatment and recommend policy changes.

*

Jason L, Benton M, Torres-Harding S, Muldowney K. The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. *Patient Educ Couns.* 2009 Nov;77(2):237-41. PMID: 19356884

CFS patients who were able to keep their expended energy close to available energy (i.e. were able to stay within their “energy envelope”) experienced significant improvements in physical functioning and fatigue severity.

*

Weinstein AA, Drinkard BM, Diao G, Furst G, Dale JK, Straus SE, Gerber LH. Exploratory analysis of the relationships between aerobic capacity and self-reported fatigue in patients with rheumatoid arthritis, polymyositis, and chronic fatigue syndrome. *PM R.* 2009 Jul;1(7):620-8. PMID: 19627955

Patients with CFS have significantly decreased aerobic capacity. Self-reports of physical activity predicted VO₂(peak), and may be used as an indicator of activity-based aerobic capacity. Self-reports of fatigue, however, did not correlate with VO₂(peak) and hence are assessing something other than an index of aerobic capacity.



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Thambirajah AA, Sleigh K, Stiver HG, Chow AW. Differential heat shock protein responses to strenuous standardized exercise in chronic fatigue syndrome patients and matched healthy controls. *Clin Invest Med*. 2008 Dec 1;31(6):E319-27. PMID: 19032901

Heat shock protein expression following exercise is abnormal in CFS, suggesting an abnormal response to oxidative stress. This has potential of serving as a biomarker.

*

Patrick Neary J, Roberts AD, Leavins N, Harrison MF, Croll JC, Sexsmith JR. Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome. *Clin Physiol Funct Imaging*. 2008 Nov;28(6):364-72. PMID: 18671793

Decreased cerebral oxygenation and blood flow may make contribute to the reduced exercise abilities in CFS.

*

Nijs J, Almond F, De Becker P, Truijen S, Paul L. Can exercise limits prevent post-exertional malaise in chronic fatigue syndrome? An uncontrolled clinical trial. *Clin Rehabil*. 2008 May;22(5):426-35. PMID: 18441039

Limiting both the intensity and duration of exercise prevents important health status changes following a walking exercise in people with CFS, but was unable to prevent short-term symptom increases.

*

Nijs J, Zwinnen K, Meeusen R, de Geus B, De Meirleir K. Comparison of two exercise testing protocols in patients with chronic fatigue syndrome. *J Rehabil Res Dev*. 2007;44(4):553-9. PMID: 18247252

CFS patients engaging in a stepwise exercise protocol had lower mechanical efficiency (ratio peak workload/peak oxygen uptake) than those engaging in a linear exercise protocol.

*

Nijs J, Demol S, Wallman K. Can submaximal exercise variables predict peak exercise performance in women with chronic fatigue syndrome? *Arch Med Res.* 2007 Apr;38(3):350-3. PMID: 17350488

This study aimed at examining whether physiological exercise variables at the submaximal level, defined as 75% of the age-predicted target heart rate, are able to predict peak exercise performance in women with chronic fatigue syndrome (CFS).

*

Yoshiuchi K, Cook DB, Ohashi K, Kumano H, Kuboki T, Yamamoto Y, Natelson BH. A real-time assessment of the effect of exercise in chronic fatigue syndrome. *Physiol Behav.* 2007 Dec 5;92(5):963-8. PMID: 17655887

CFS patients experienced increased physical symptoms after exercise, on average with a five-day delay. Psychological symptoms and cognitive functioning did not change after exercise.

*

Nijs J, Meeus M, De Meirleir K. Chronic musculoskeletal pain in chronic fatigue syndrome: recent developments and therapeutic implications. *Man Ther.* 2006 Aug;11(3):187-91. PMID: 16781183

CFS sufferers respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain, postexertional malaise, and the decrease in pain threshold following graded exercise in CFS patients.

*

Cook DB, Nagelkirk PR, Poluri A, Mores J, Natelson BH. The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome. *Arthritis Rheum.* 2006 Oct;54(10):3351-62. PMID: 17009309

In the overall sample, there were no significant differences in cardiorespiratory parameters between the CFS only group and the controls. However, the CFS plus FM



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group exhibited lower ventilation, lower end-tidal CO₂, and higher ventilatory equivalent of carbon dioxide compared with controls, and slower increases in heart rate compared with both patients with CFS only and controls. Peak oxygen consumption, ventilation, and workload were lower in the CFS plus FM group. Subjects in both the CFS only group and the CFS plus FM group rated exercise as more effortful than did controls.

*

Nijs J, Meeus M, McGregor NR, Meeusen R, de Schutter G, van Hoof E, de Meirleir K. Chronic fatigue syndrome: exercise performance related to immune dysfunction. *Med Sci Sports Exerc.* 2005 Oct;37(10):1647-54. PMID: 16260962

There appears to be an association between intracellular immune deregulation and exercise performance in patients with CFS.

*

Jammes Y, Steinberg JG, Mambrini O, Brégeon F, Delliaux S. Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise. *J Intern Med.* 2005 Mar;257(3):299-310. PMID: 15715687

Following exercise, CFS patients have lengthened and accentuated oxidative stress together with marked alterations of the muscle membrane excitability.

*

Nijs J, De Meirleir K. Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome. *In Vivo.* 2005 Nov-Dec;19(6):1013-21. PMID: 16277015

The 2'-5' oligoadenylate (2-5 A) synthetase/RNase L pathway in CFS patients appears to be both upregulated and deregulated, and this seems to be related to performance during a graded exercise stress test.

*

Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. *Dyn Med.* 2005 Oct 28;4:10. PMID: 16255779



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CFS patients who attempt to increase their activity by participating in a daily walking program have a difficult time maintaining that increase over time and usually compensate by reducing other activity.

*

Bazelmans E, Bleijenberg G, Voeten MJ, van der Meer JW, Folgering H. Impact of a maximal exercise test on symptoms and activity in chronic fatigue syndrome. *J Psychosom Res.* 2005 Oct;59(4):201-8. PMID: 16223622

After exercise, CFS patients reported fatigue for an additional two days, compared to two hours for matched sedentary controls.

*

Snell CR, Vanness JM, Strayer DR, Stevens SR. Exercise capacity and immune function in male and female patients with chronic fatigue syndrome (CFS). *In Vivo.* 2005 Mar-Apr;19(2):387-90. PMID: 15796202

Abnormal immune activity related to oxidative stress, nitric oxide related toxicity and hyperactivation of Rnase-L is related to exercise intolerance in CFS patients.

*

Whistler T, Jones JF, Unger ER, Vernon SD. Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects. *BMC Physiol.* 2005 Mar 24;5(1):5. PMID: 15790422

Following an exercise challenge, CFS patients differed from controls on a variety of genes, including chromatin and nucleosome assembly, cytoplasmic vesicles, membrane transport and G protein-coupled receptor ontologies. Differences in ion transport and ion channel activity were evident at baseline and exaggerated after exercise.

*

Nijs J, De Meirleir K. Prediction of peak oxygen uptake in patients fulfilling the 1994 CDC criteria for chronic fatigue syndrome. *Clin Rehabil.* 2004 Nov;18(7):785-92. PMID: 15573835



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A technique to predict peak oxygen uptake in CFS patients was developed.

*

Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue syndrome. *Pain*. 2004 Jun;109(3):497-9. PMID: 15157711

During exercise, normal people have higher pain thresholds and CFS patients have lower pain thresholds.

*

Nijs J, Vanherberghen K, Duquet W, De Meirleir K. Chronic fatigue syndrome: lack of association between pain-related fear of movement and exercise capacity and disability. *Phys Ther*. 2004 Aug;84(8):696-705. PMID: 15283620

This study shows a lack of correlation between kinesiophobia (fear of movement) and exercise capacity, activity limitations, or participation restrictions, at least in patients with CFS who are experiencing widespread muscle or joint pain.

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Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH. Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clin Neurophysiol*. 2004 Oct;115(10):2372-81. PMID: 15351380

CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue.

*

McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Muscle metabolism with blood flow restriction in chronic fatigue syndrome. *J Appl Physiol*. 2004 Mar;96(3):871-8. PMID: 14578362

CFS patients have evidence of hyperemic flow and reduced oxygen delivery, but this does not seem to result in disturbed muscle metabolism.

*

Nijs J, De Meirleir K, Wolfs S, Duquet W. Disability evaluation in chronic fatigue syndrome: associations between exercise capacity and activity limitations/participation restrictions. *Clin Rehabil.* 2004 Mar;18(2):139-48. PMID: 15053122

These results suggest a moderate association between exercise capacity and activity limitations/participation restrictions in patients with CFS. The observed correlations lack strength to predict activity limitations/ participation restriction based on exercise capacity parameters.

*

Sorensen B, Streib JE, Strand M, Make B, Giclas PC, Fleshner M, Jones JF. Complement activation in a model of chronic fatigue syndrome. *J Allergy Clin Immunol.* 2003 Aug;112(2):397-403. PMID: 12897748

Exercise challenge induced significant increases of the complement split product C4a, but not C3a or C5a, at 6 hours after exercise only in the CFS group. This has potential of serving as a biomarker.

*

Vanness JM, Snell CR, Strayer DR, Dempsey L 4th, Stevens SR. Subclassifying chronic fatigue syndrome through exercise testing. *Med Sci Sports Exerc.* 2003 Jun;35(6):908-13. PMID: 12783037

Severely affected CFS patients are more impaired during exercise stress tests in terms of peak systolic blood pressure and peak heart rate.

*

Snell CR, Vanness JM, Strayer DR, Stevens SR. Physical performance and prediction of 2-5A synthetase/RNase L antiviral pathway activity in patients with chronic fatigue syndrome. *In Vivo.* 2002 Mar-Apr;16(2):107-9. PMID: 12073768

Seventy-three CFS patients performed a graded exercise test to voluntary exhaustion. Forty-six patients had elevated RNase L levels. The elevated RNase L group had a lower peak V02 and duration than the normal group, but a higher KPS. Both Rnase L and exercise intolerance have potential as biomarkers for CFS.



Paradigm Change

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Ohashi K, Yamamoto Y, Natelson BH. Activity rhythm degrades after strenuous exercise in chronic fatigue syndrome. *Physiol Behav.* 2002 Sep;77(1):39-44. PMID: 12213500

CFS patients had an abnormal lengthening ($P < .05$) of mean circadian period (MCP) after exercise that was longer than 24 hours.

*

Farquhar WB, Hunt BE, Taylor JA, Darling SE, Freeman R. Blood volume and its relation to peak O_2 consumption and physical activity in patients with chronic fatigue. *Am J Physiol Heart Circ Physiol.* 2002 Jan;282(1):H66-71. PMID: 11748048

CFS patients tend to have low blood volume and low peak oxygen consumption, and this seems to be related to their exercise intolerance.

*

Inbar O, Dlin R, Rotstein A, Whipp BJ. Physiological responses to incremental exercise in patients with chronic fatigue syndrome. *Med Sci Sports Exerc.* 2001 Sep;33(9):1463-70. PMID: 11528333

CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values at peak exercise, compared with the control group.

*

Jason LA, Melrose H, Lerman A, Burroughs V, Lewis K, King CP, Frankenberry EL. Managing chronic fatigue syndrome: overview and case study. *AAOHN J.* 1999 Jan;47(1):17-21. PMID: 10205371

The basic principles of envelope theory are explained. By not overexerting themselves, people with CFS can avoid the setbacks and relapses that commonly occur in response to overexertion while increasing their tolerance to activity.

*



Paradigm Change

McCully KK, Natelson BH. Impaired oxygen delivery to muscle in chronic fatigue syndrome. *Clin Sci (Lond)*. 1999 Nov;97(5):603-8; discussion 611-3. PMID: 10545311

Compared to healthy controls, CFS patients suffered abnormally reduced time constant of oxygen delivery and oxidative metabolism following exercise.

*

Mullis R, Campbell IT, Wearden AJ, Morriss RK, Pearson DJ. Prediction of peak oxygen uptake in chronic fatigue syndrome. *Br J Sports Med*. 1999 Oct;33(5):352-6. PMID: 10522640

Using a simple to administer maximal exercise test on a cycle ergometer, it is possible to predict accurately the VO₂peak of a patient with CFS from peak work rate alone. This value can then be used as an aid to setting appropriate exercise intensity for a rehabilitation programme.

*

Paul L, Wood L, Behan WM, Maclaren WM. Demonstration of delayed recovery from fatiguing exercise in chronic fatigue syndrome. *Eur J Neurol*. 1999 Jan;6(1):63-9. PMID: 10209352

Throughout a period of exercise, patients were able to exercise less than controls. Recovery was prolonged in the patient group, however, with a significant difference compared to initial amount of exercise being evident during the recovery phase after exercise ($P = 0.001$) and also at 24 h ($P < 0.001$). These findings support the clinical complaint of delayed recovery after exercise in patients with CFS.

*

LaManca JJ, Sisto SA, DeLuca J, Johnson SK, Lange G, Pareja J, Cook S, Natelson BH. Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome. *Am J Med*. 1998 Sep 28;105(3A):59S-65S. PMID: 9790484

After a physically demanding exercise, CFS subjects demonstrated impaired cognitive processing compared with healthy individuals.

*



Paradigm Change

Blackwood SK, MacHale SM, Power MJ, Goodwin GM, Lawrie SM. Effects of exercise on cognitive and motor function in chronic fatigue syndrome and depression. *J Neurol Neurosurg Psychiatry*. 1998 Oct;65(4):541-6. PMID: 9771781

After exertion, patients with chronic fatigue syndrome showed a greater decrease than healthy controls on everyday tests of focused and sustained attention, as well as greater deterioration than depressed patients on the focused attention task.

*

Lane RJ, Barrett MC, Woodrow D, Moss J, Fletcher R, Archard LC. Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry*. 1998 Mar;64(3):362-7. PMID: 9527150

Muscle histometry in patients with chronic fatigue syndrome generally did not show the changes expected as a result of inactivity. However, patients with abnormal lactate responses to exercise had a significantly lower proportion of mitochondria rich type 1 muscle fibres.

*

Fischler B, Dendale P, Michiels V, Cluydts R, Kaufman L, De Meirleir K. Physical fatigability and exercise capacity in chronic fatigue syndrome: association with disability, somatization and psychopathology. *J Psychosom Res*. 1997 Apr;42(4):369-78. PMID: 9160276

The authors present evidence against an association in CFS between avoidance of physically demanding tasks and early anaerobic metabolism during effort.

*

Kent-Braun JA, Sharma KR, Weiner MW, Massie B, Miller RG. Central basis of muscle fatigue in chronic fatigue syndrome. *Neurology*. 1993 Jan;43(1):125-31.

Voluntary activation of the tibialis was significantly lower in CFS patients during maximal sustained exercise.

*



Paradigm Change

Wong R, Lopaschuk G, Zhu G, Walker D, Catellier D, Burton D, Teo K, Collins-Nakai R, Montague T. Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by ³¹P nuclear magnetic resonance spectroscopy. *Chest*. 1992 Dec;102(6):1716-22. PMID: 1446478

CFS patients reach exhaustion much more rapidly than normal subjects, at which point they also have relatively reduced intracellular concentrations of ATP. These data suggest a defect of oxidative metabolism with a resultant acceleration of glycolysis in the working skeletal muscles of CFS patients.

*

Montague TJ, Marrie TJ, Klassen GA, Bewick DJ, Horacek BM. Cardiac function at rest and with exercise in the chronic fatigue syndrome. *Chest*. 1989 Apr;95(4):779-84. PMID: 2924607

Patients with chronic fatigue syndrome have normal resting cardiac function but a markedly abbreviated exercise capacity characterized by slow acceleration of heart rate and fatigue of exercising muscles long before peak heart rate is achieved.

CFS AND EXERCISE INTOLERANCE

MEDIA COVERAGE

May 17, 2011

The Wall Street Journal

Health Blog

Study Blowback Shows Controversy Over Chronic Fatigue Syndrome

By Katherine Hobson

<http://blogs.wsj.com/health/2011/05/17/study-blowback-shows-controversy-over-chronic-fatigue-syndrome/>

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April 15, 2011

The Edinburgh Evening News

Is Exercise Always Good For the Body?

By Adam Morris

<http://edinburghnews.scotsman.com/features/is-exercise-always-good-for.6752231.jp>

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March 14, 2011

The New York Times

Studying a Fatigue Illness

Letters

http://www.nytimes.com/2011/03/15/health/15letters-STUDYINGAFAT_LETTERS.html?scp=1&sq=%22David%20Tuller%22%20chronic&st=cse

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February 18, 2011

The Wall Street Journal

Health Blog

This Study on Chronic-Fatigue Syndrome Has Nothing to Do with XMRV
By Katherine Hobson

<http://blogs.wsj.com/health/2011/02/18/this-study-on-chronic-fatigue-syndrome-has-nothing-to-do-with-xmrv/>

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February 17, 2011
The New York Times
Psychotherapy Eases Chronic Fatigue Syndrome, Study Finds
By David Tuller

http://www.nytimes.com/2011/02/18/health/research/18fatigue.html?%2334;chronic%20fatigue%20syndrome=&_r=1&sq=&st=cse&%2334;=&scp=5&pagewanted=print

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